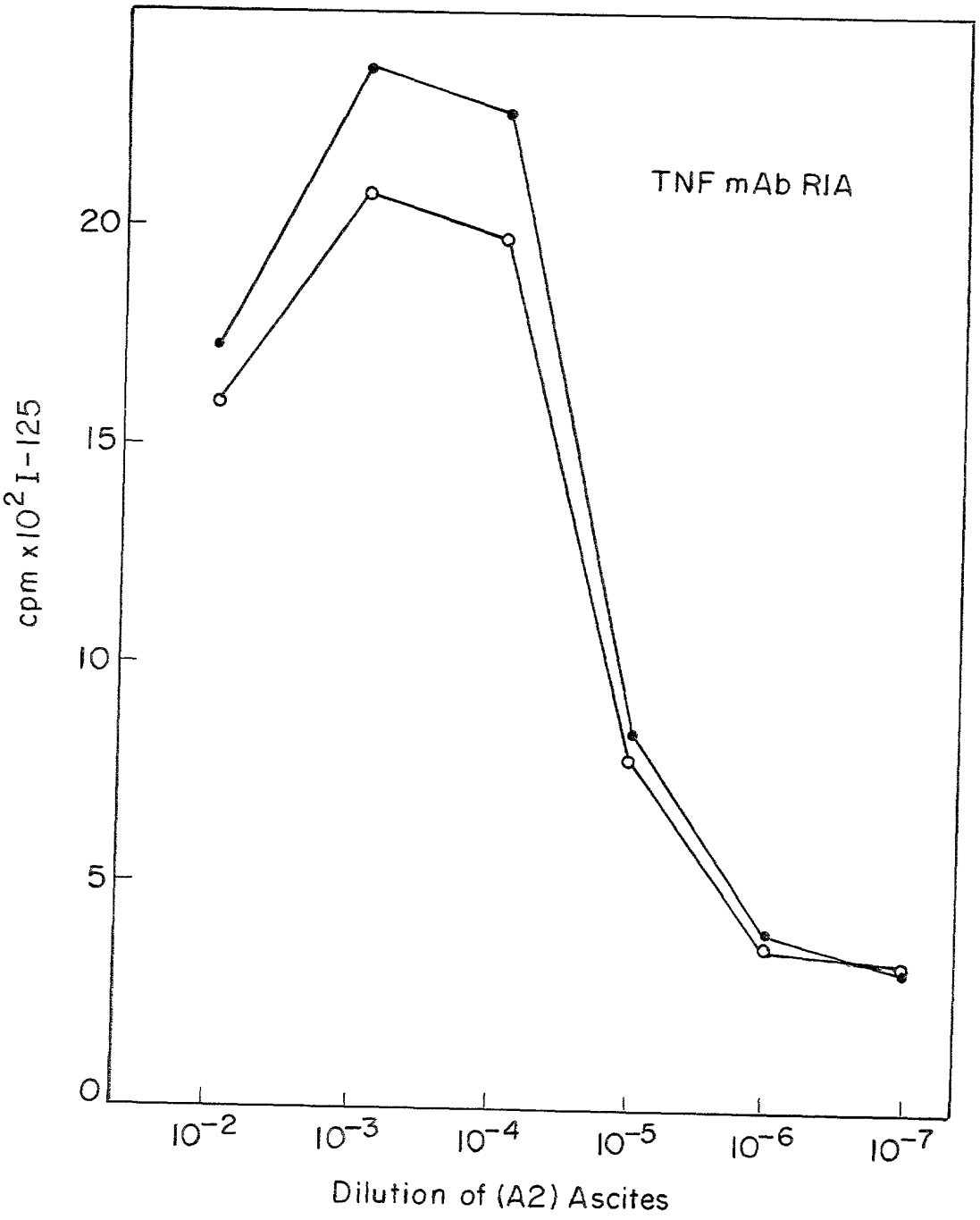

TNF mAb RIA
cpm x10² I-125
20
15
10
5
0
10⁻²
10⁻³
10⁻⁴
10⁻⁵
10⁻⁶
10⁻⁷
Dilution of (A2) Ascites

FIG. 1

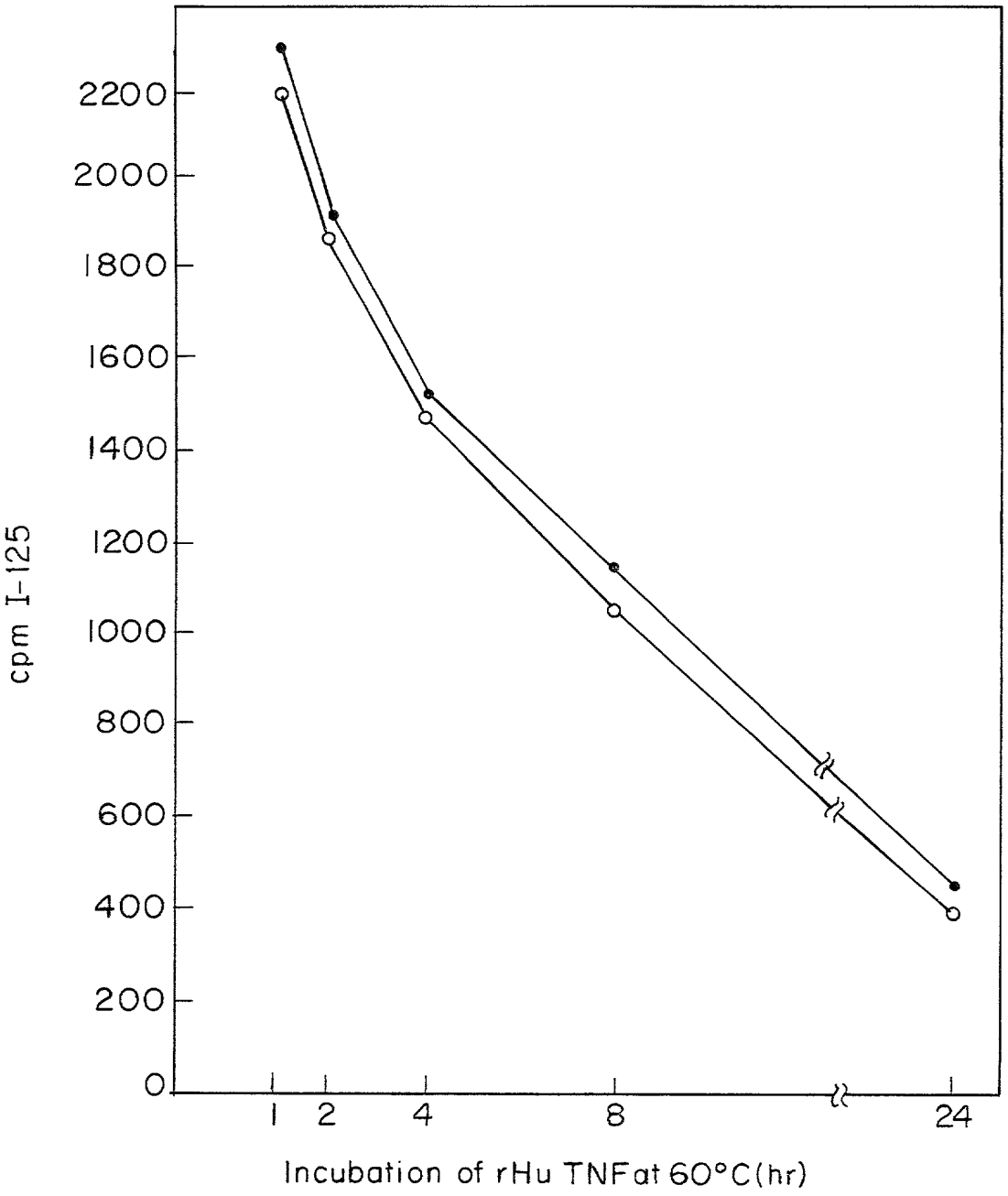

2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
cpm I-125
1
2
4
8
24
Incubation of rHu TNF at 60°C (hr)

FIG. 2

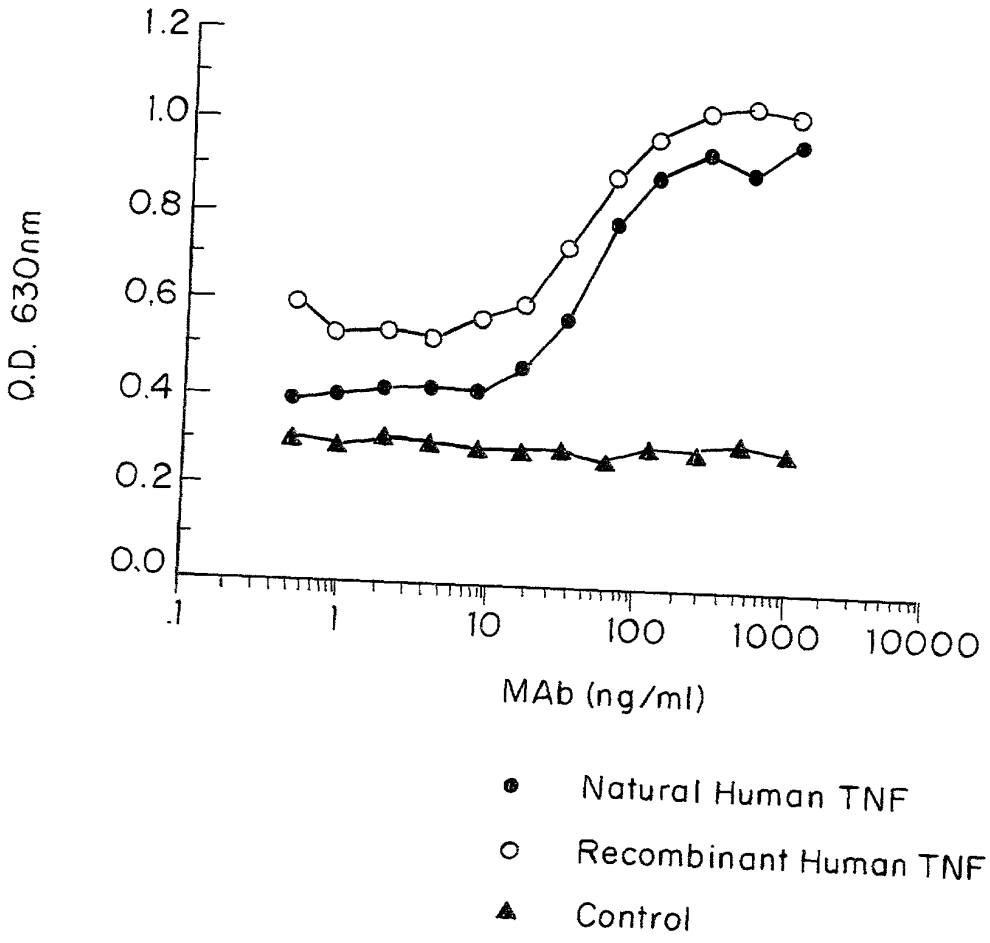

1.2
1.0
0.8
0.6
0.4
0.2
0.0
O.D. 630nm
.1
1
10
100
1000
10000
MAb (ng/ml)
Natural Human TNF
Recombinant Human TNF
Control

FIG. 3

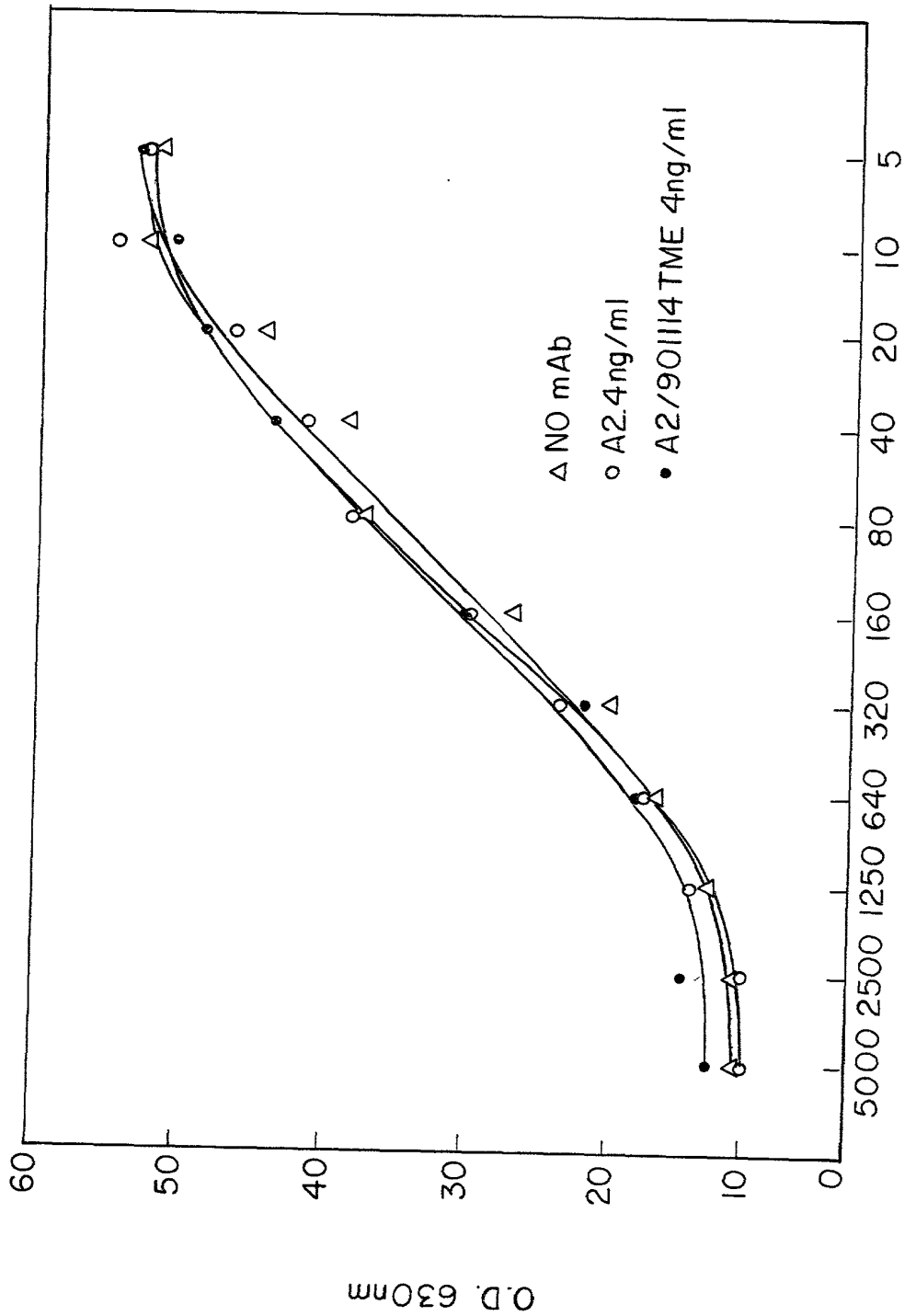

O.D. 630nm
60
50
40
30
20
10
0
5000 2500 1250 640 320 160 80 40 20 10 5
rHuLT (pg/ml)
Δ NO mAb
o A2.4ng/ml
• A2/90114 TME 4ng/ml

FIG. 4

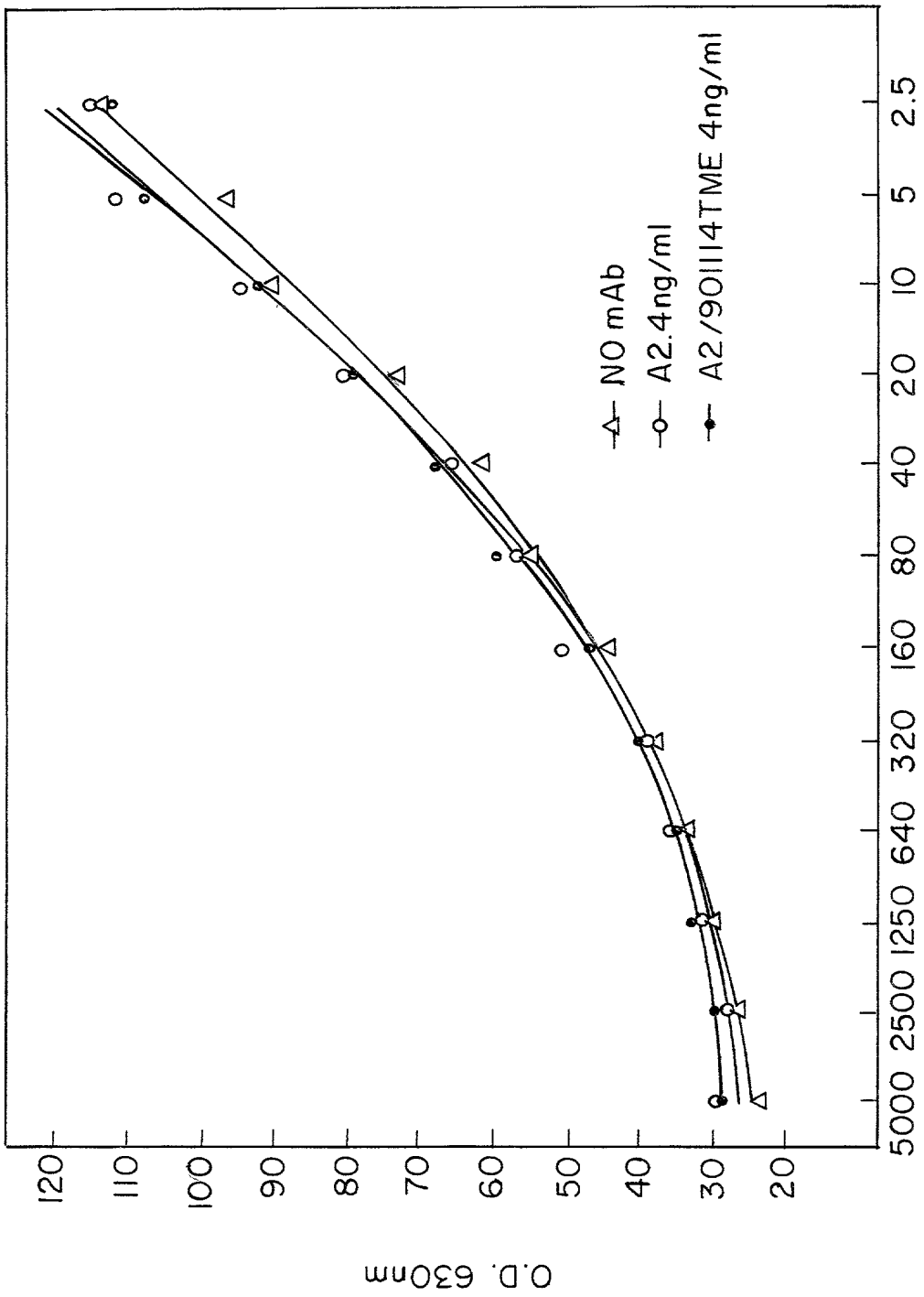

O.D. 630nm
120
110
100
90
80
70
60
50
40
30
20
5000 2500 1250 640 320 160 80 40 20 10 5 2.5
murine TNF (pg/ml)
NO mAb
A2.4ng/ml
A2/9011114TME 4ng/ml

FIG. 5

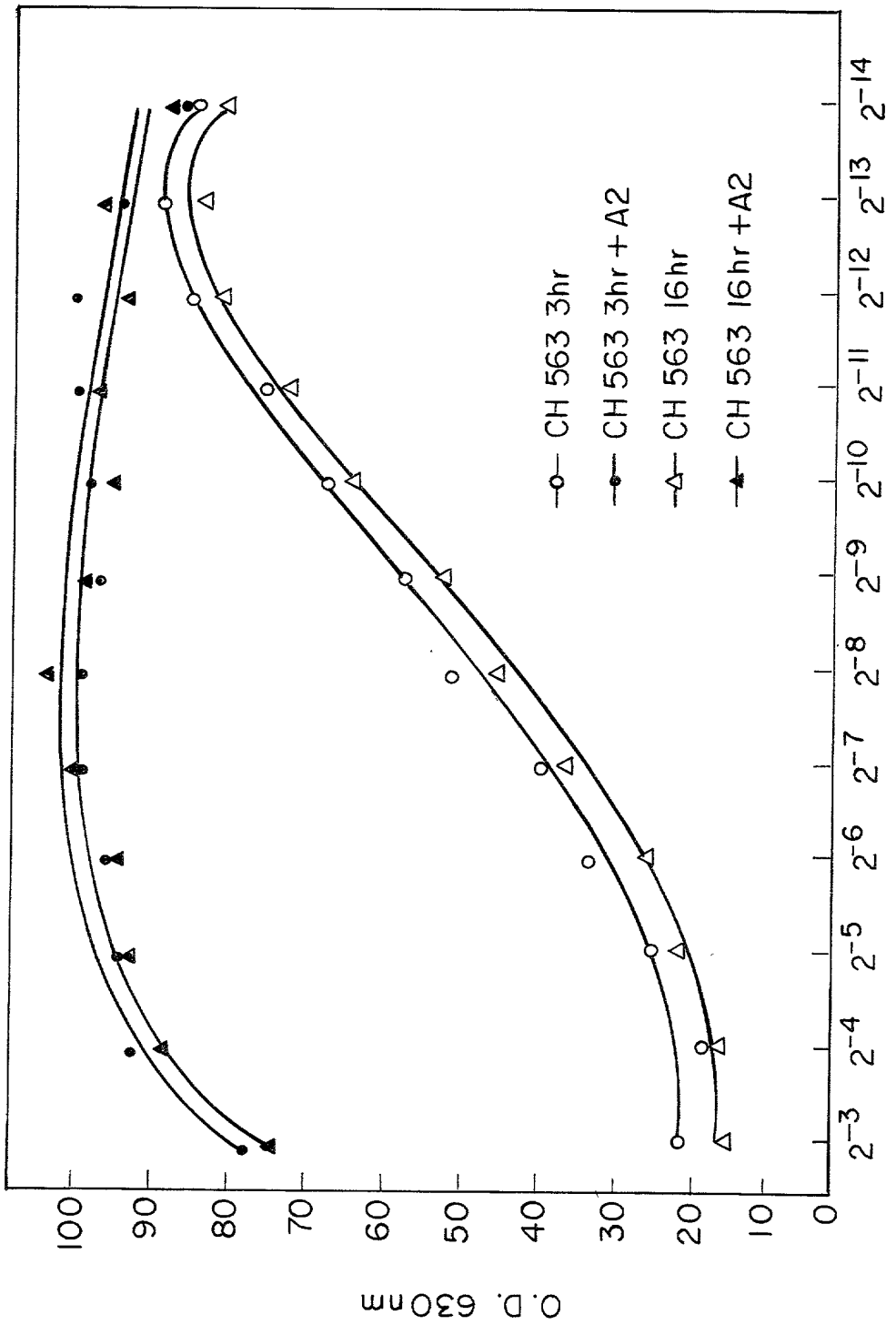

O.D. 630nm
100
90
80
70
60
50
40
30
20
10
0
2^{-3} 2^{-4} 2^{-5} 2^{-6} 2^{-7} 2^{-8} 2^{-9} 2^{-10} 2^{-11} 2^{-12} 2^{-13} 2^{-14}
Dilution
CH 563 3hr
CH 563 3hr + A2
CH 563 16hr
CH 563 16hr + A2

FIG. 6

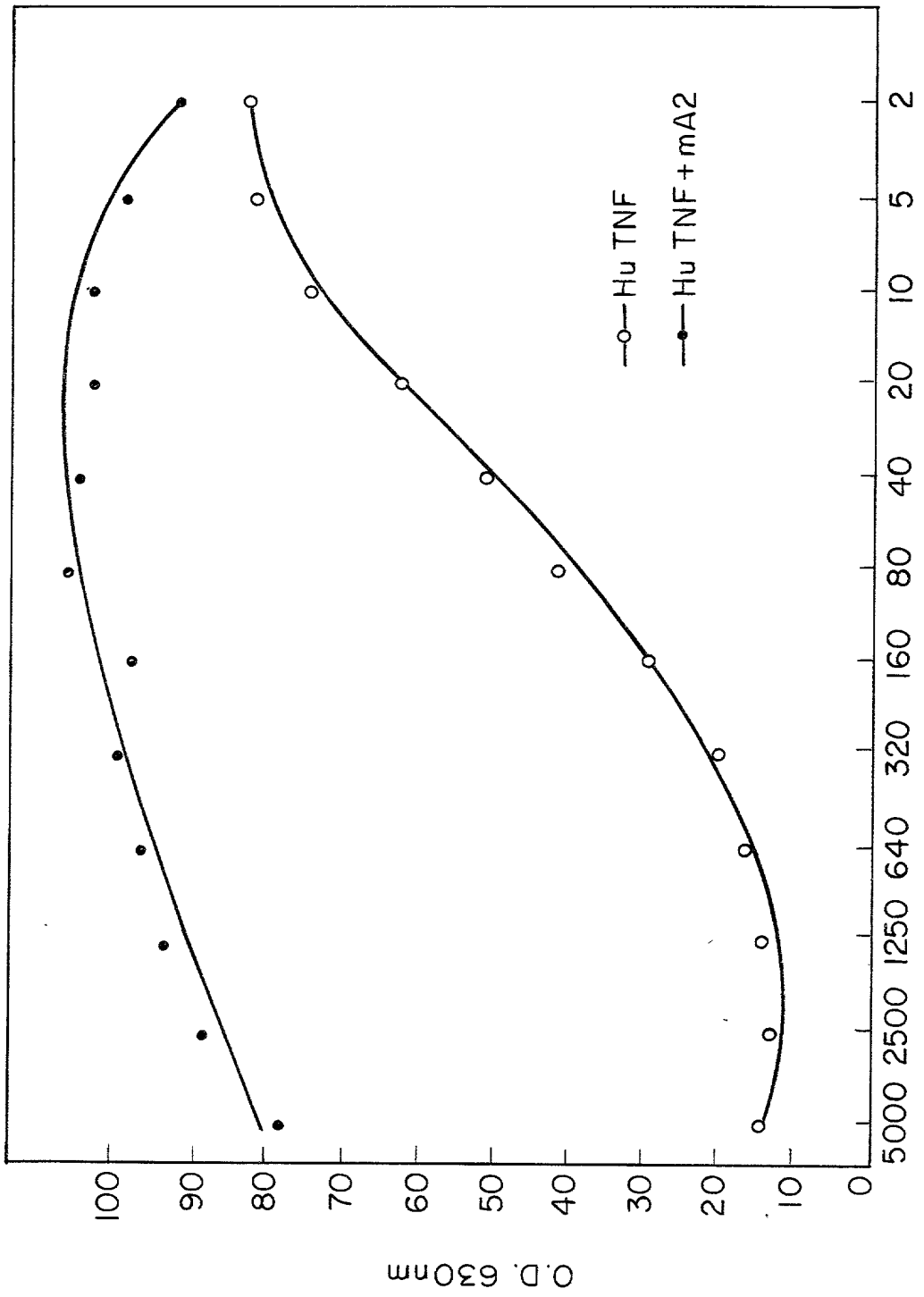
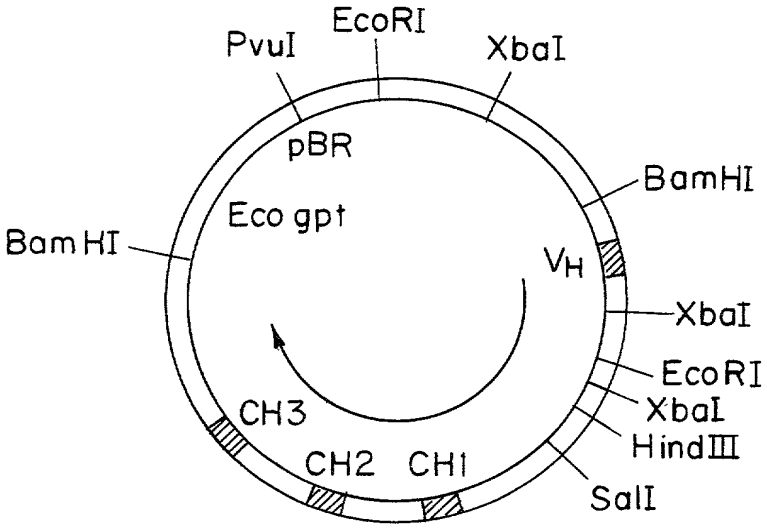
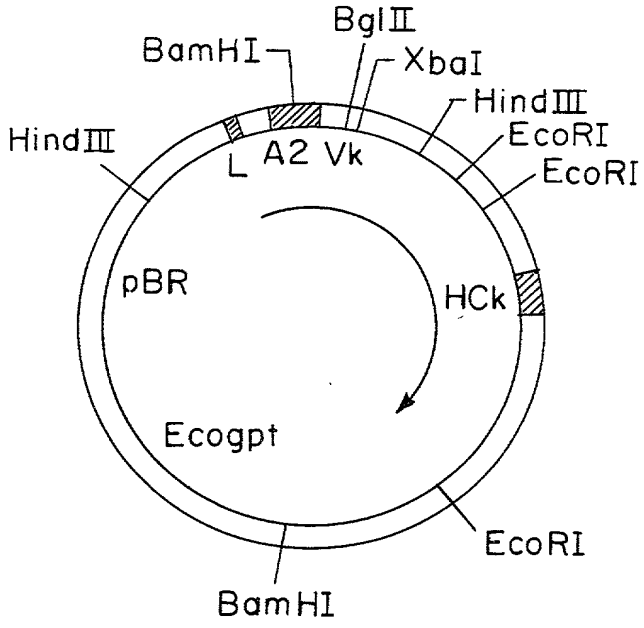

O.D. 630nm
100
90
80
70
60
50
40
30
20
10
0
5000 2500 1250 640 320 160 80 40 20 10 5 2
rHu TNF (pg/ml)
Hu TNF
Hu TNF + mA2

FIG. 7



pA2HG1apgpt

FIG. 8A



pA2HuKapgpt

FIG. 8B

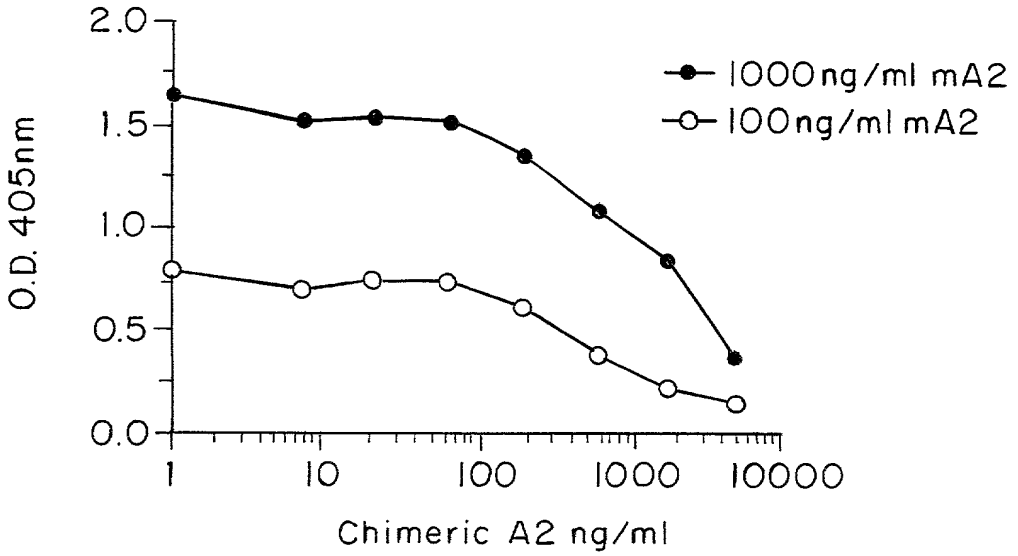

2.0
1.5
1.0
0.5
0.0
O.D. 405nm
1000ng/ml mA2
100ng/ml mA2
1
10
100
1000
10000
Chimeric A2 ng/ml

FIG. 9A

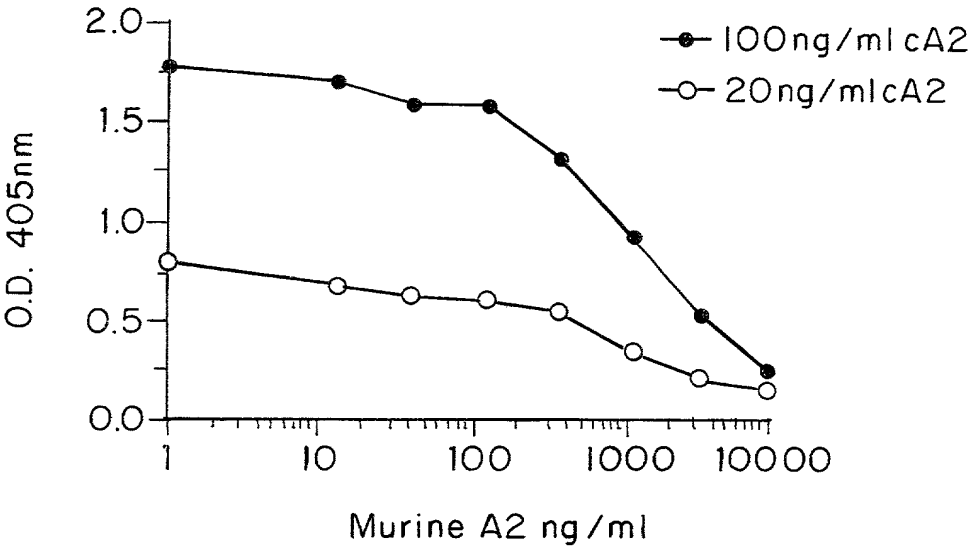

2.0
1.5
1.0
0.5
0.0
O.D. 405nm
100ng/ml cA2
20ng/ml cA2
1
10
100
1000
10000
Murine A2 ng/ml

FIG. 9B

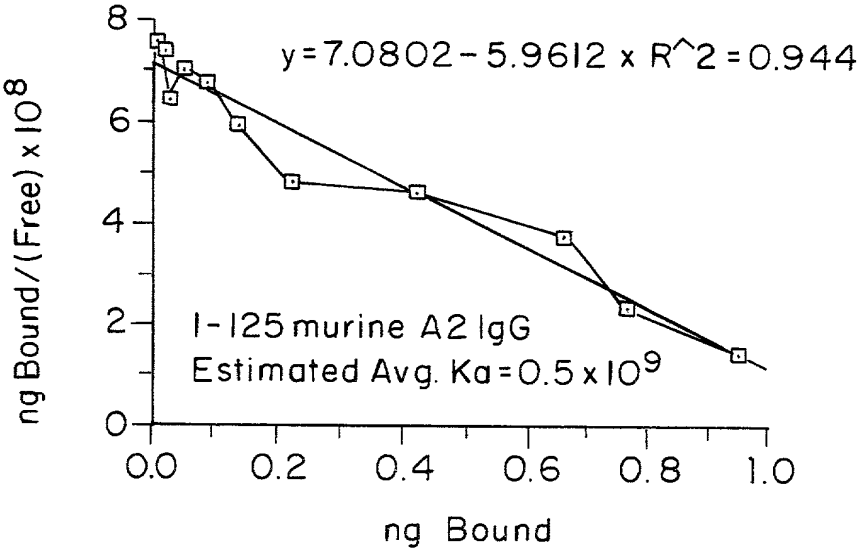


FIG. 10A

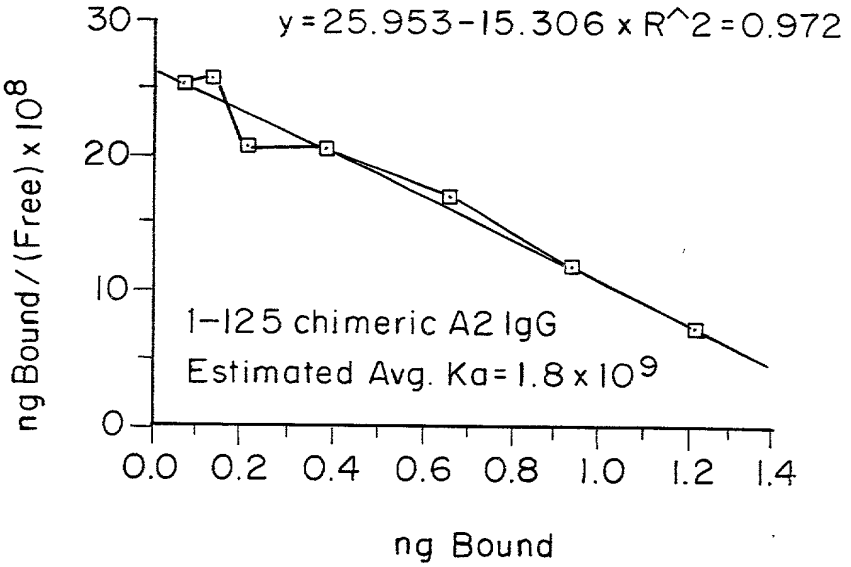


FIG. 10B

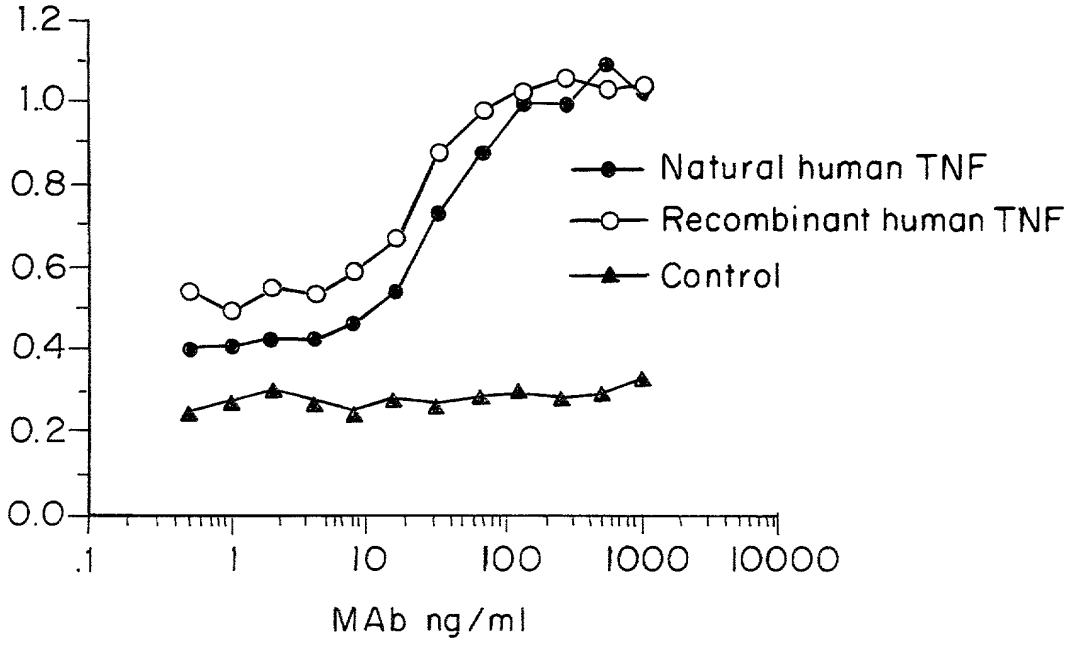

1.2
1.0
0.8
0.6
0.4
0.2
0.0
.1
1
10
100
1000
10000
MAb ng/ml
Natural human TNF
Recombinant human TNF
Control

FIG. 11

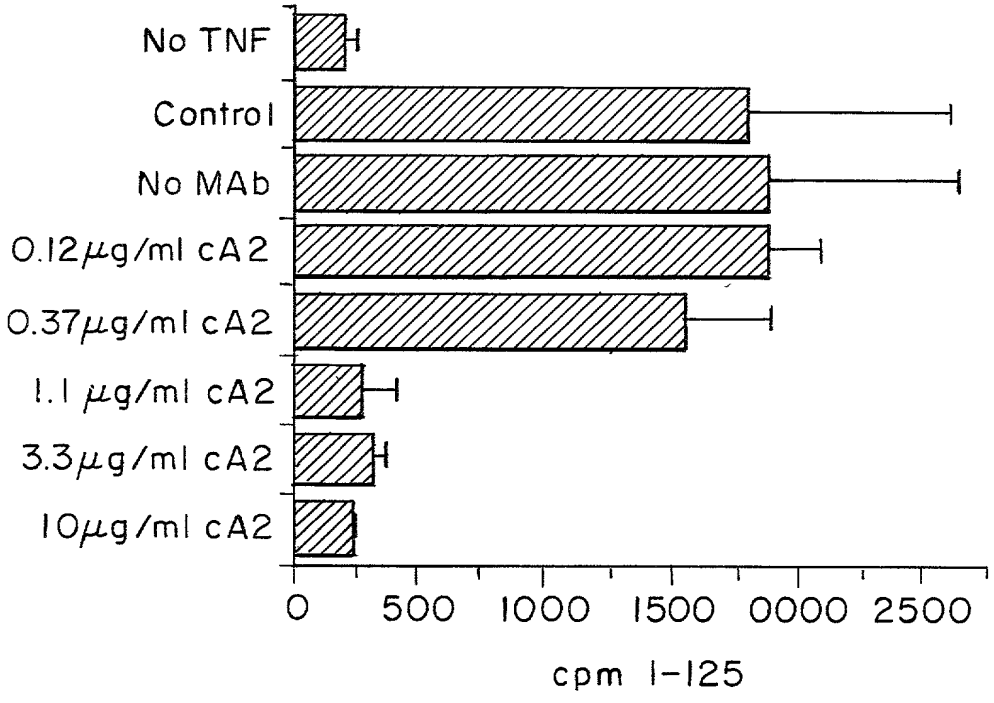

No TNF
Control
No MAb
0.12μg/ml cA2
0.37μg/ml cA2
1.1 μg/ml cA2
3.3μg/ml cA2
10μg/ml cA2
0
500
1000
1500
0000
2500
cpm I-125

FIG. 12

```
1                                                   10
Val Arg Ser Ser Ser Arg Thr Pro Ser Asp Lys Pro Val Ala His Val Val Ala Asn Pro

21                                                  30
Gln Ala Glu Gly Gln Leu Gln Trp Leu Asn Arg Arg Ala Asn Ala Leu Leu Ala Asn Gly

41                                                  50
Val Glu Leu Arg Asp Asn Gln Leu Val Val Pro Ser Glu Gly Leu Tyr Leu Ile Tyr Ser

61                                                  70
Gln Val Leu Phe Lys Gly Gln Gly Cys Pro Ser Thr His Val Leu Leu Thr His Thr Ile

81                                                  90
Ser Arg Ile Ala Val Ser Tyr Gln Thr Lys Val Asn Leu Leu Ser Ala Ile Lys Ser Pro

101                                                 110
Cys Gln Arg Glu Thr Pro Glu Gly Ala Glu Ala Lys Pro Trp Tyr Glu Pro Ile Tyr Leu

121                                                 130
Gly Gly Val Phe Gln Leu Glu Lys Gly Asp Arg Leu Ser Ala Glu Ile Asn Arg Pro Asp

141                                                 150
Tyr Leu Asp Phe Ala Glu Ser Gly Gln Val Tyr Phe Gly Ile Ile Ala Leu
```

FIG. 13

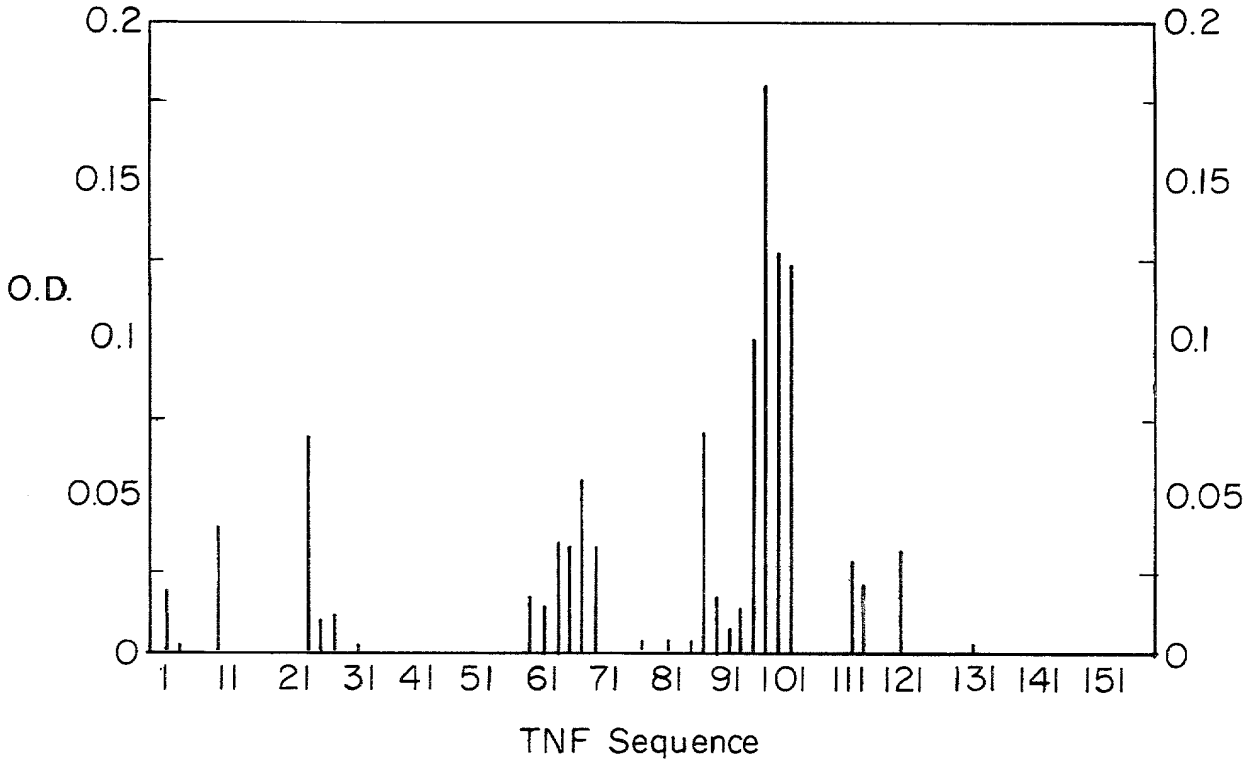


FIG. 14A

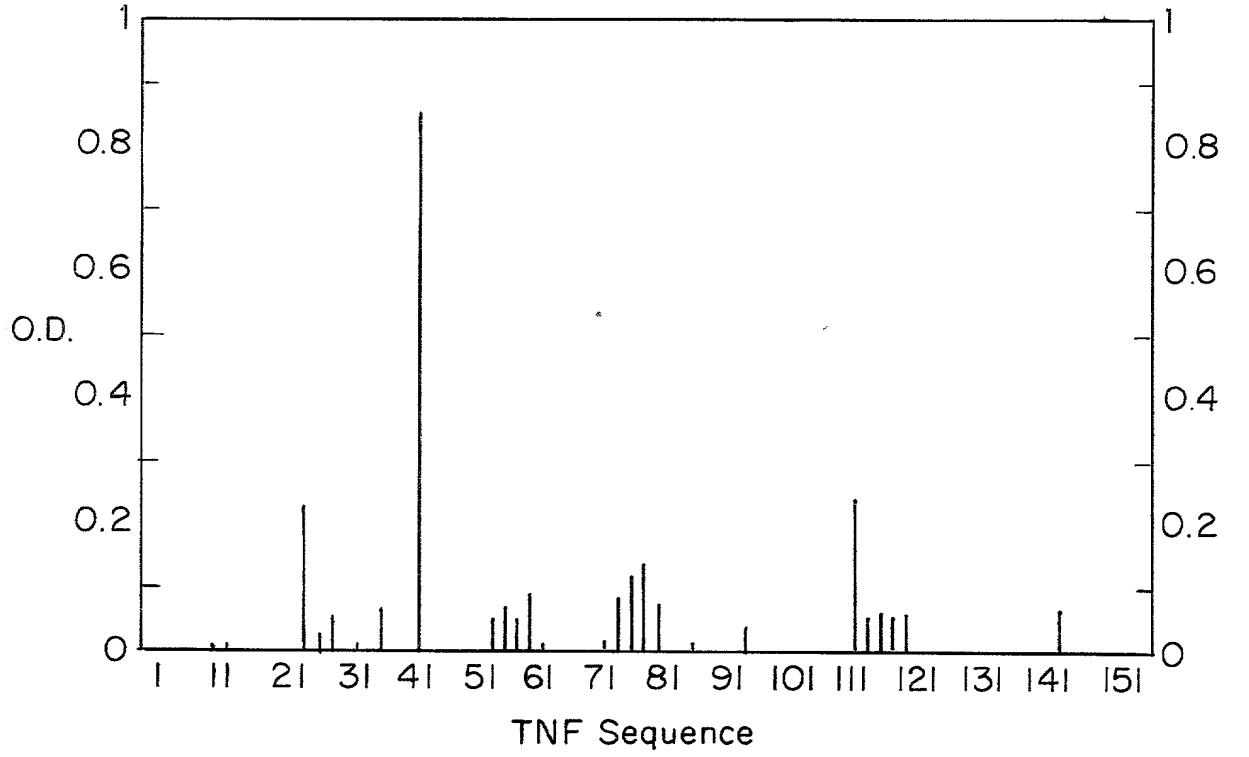


FIG. 14B

1 10
Val Arg Ser Ser Ser Arg Thr Pro Ser Asp Lys Pro Val Ala His Val Val Ala Asn Pro

21 30
Gln Ala Glu Gly Gln Leu Gln Trp Leu Asn Arg Arg Ala Asn Ala Leu Leu Ala Asn Gly

41 50
Val Glu Leu Arg Asp Asn Gln Leu Val Val Pro Ser Glu Gly Leu Tyr Leu Ile Tyr Ser

61 70
Gln Val Leu Phe Lys Gly Gln Gly Cys Pro Ser Thr His Val Leu Leu Thr His Thr Ile

81 90
Ser Arg Ile Ala Val Ser Tyr Gln Thr Lys Val Asn Leu Leu Ser Ala Ile Lys Ser Pro

101 110
Cys Gln Arg Glu Thr Pro Glu Gly Ala Glu Ala Lys Pro Trp Tyr Glu Pro Ile Tyr Leu

121 130
Gly Gly Val Phe Gln Leu Glu Lys Gly Asp Arg Leu Ser Ala Glu Ile Asn Arg Pro Asp

141 150
Tyr Leu Asp Phe Ala Glu Ser Gly Gln Val Tyr Phe Gly Ile Ile Ala Leu

FIG. 15

GACATCTTGCTGACTCAGTCTCCAGCCATCCTGTCTGTGAGTCCAGGAGAAAGAGTCAGT
AspIleLeuLeuThrGlnSerProAlaIleLeuSerValSerProGlyGluArgValSer

TTCTCCTGCAGGGCCAGTCAGTTCGTTGGCTCAAGCATCCACTGGTATCAGCAAAGAACA
PheSerCysArgAlaSerGlnPheValGlySerSerIleHisTrpTyrGlnGlnArgThr

AATGGTTCTCCAAGGCTTCTCATAAAGTATGCTTCTGAGTCTATGTCTGGGATCCCTTCC
AsnGlySerProArgLeuLeuIleLysTyrAlaSerGluSerMetSerGlyIleProSer

AGGTTTAGTGGCAGTGGATCAGGGACAGATTTTACTCTTAGCATCAACACTGTGGAGTCT
ArgPheSerGlySerGlySerGlyThrAspPheThrLeuSerIleAsnThrValGluSer

GAAGATATTGCAGATTATTACTGTCAAGAAAGTCATAGCTGGCCATTCACGTTCGGCTCG
GluAspIleAlaAspTyrTyrCysGlnGlnSerHisSerTrpProPheThrPheGlySer

GGGACAAATTTGGAAGTAAAA
GlyThrAsnLeuGluValLys

FIG. 16A

GAAGTGAAGCTTGAGGAGTCTGGAGGAGGCTTGGTGCAACCTGGAGGATCCATGAAACTC
GluValLysLeuGluGluSerGlyGlyGlyLeuValGlnProGlyGlySerMetLysLeu

TCCTGTGTTGCCTCTGGATTCATTTTCAGTAACCACTGGATGAACTGGGTCCGCCAGTCT
SerCysValAlaSerGlyPheIlePheSerAsnHisTrpMetAsnTrpValArgGlnSer

CCAGAGAAGGGGCTTGAGTGGGTTGCTGAAATTAGATCAAAATCTATTAATTCTGCAACA
ProGluLysGlyLeuGluTrpValAlaGluIleArgSerLysSerIleAsnSerAlaThr

CATTATGCGGAGTCTGTGAAAGGGAGGTTCACCATCTCAAGAGATGATTCCAAAAGTGCT
HisTyrAlaGluSerValLysGlyArgPheThrIleSerArgAspAspSerLysSerAla

GTGTACCTGCAAATGACCGACTTAAGAACTGAAGACACTGGCGTTTATTACTGTTCCAGG
ValTyrLeuGlnMetThrAspLeuArgThrGluAspThrGlyValTyrTyrCysSerArg

AATTACTACGGTAGTACCTACGACTACTGGGGCCAAGGCACCACTCTCACAGTGTCC
AsnTyrTyrGlySerThrTyrAspTyrTrpGlyGlnGlyThrThrLeuThrValSer

FIG. 16B

Docket No.: 0975.1005-018
Title: METHODS OF TREATING HEPATITIS ....
Inventors: Junming Le, *et al*

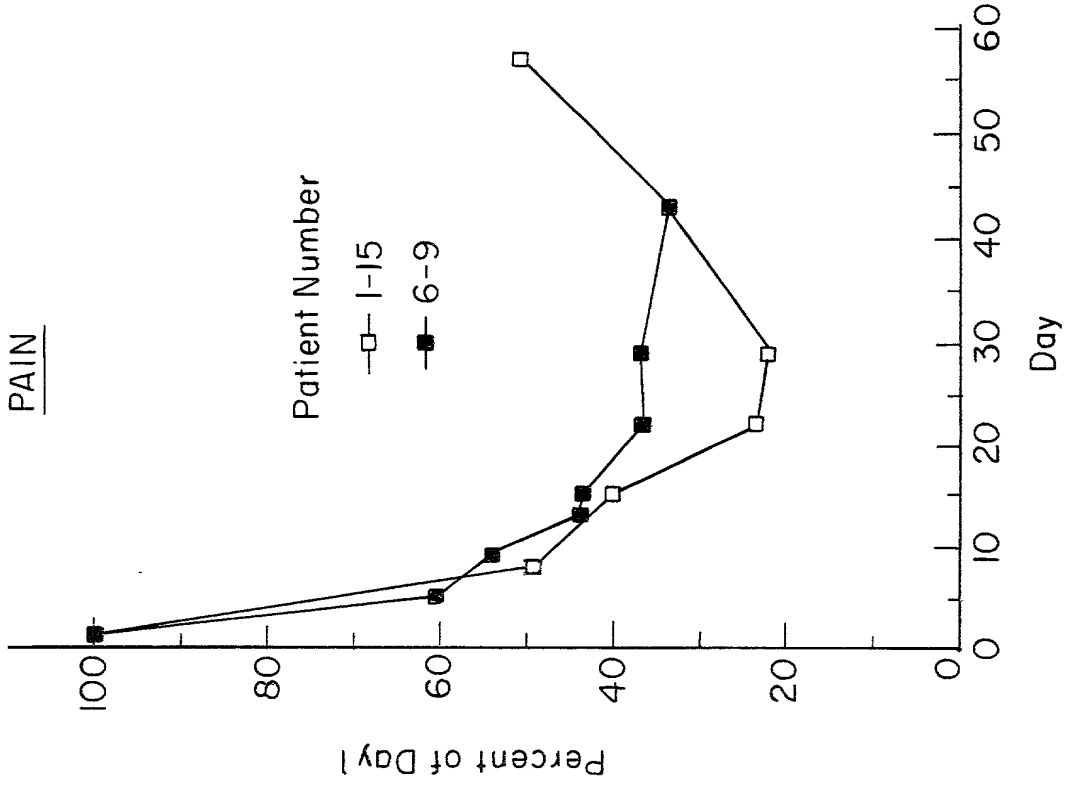

PAIN
Patient Number
1-15
6-9
Percent of Day 1
Day
0
10
20
30
40
50
60
20
40
60
80
100

FIG. 18

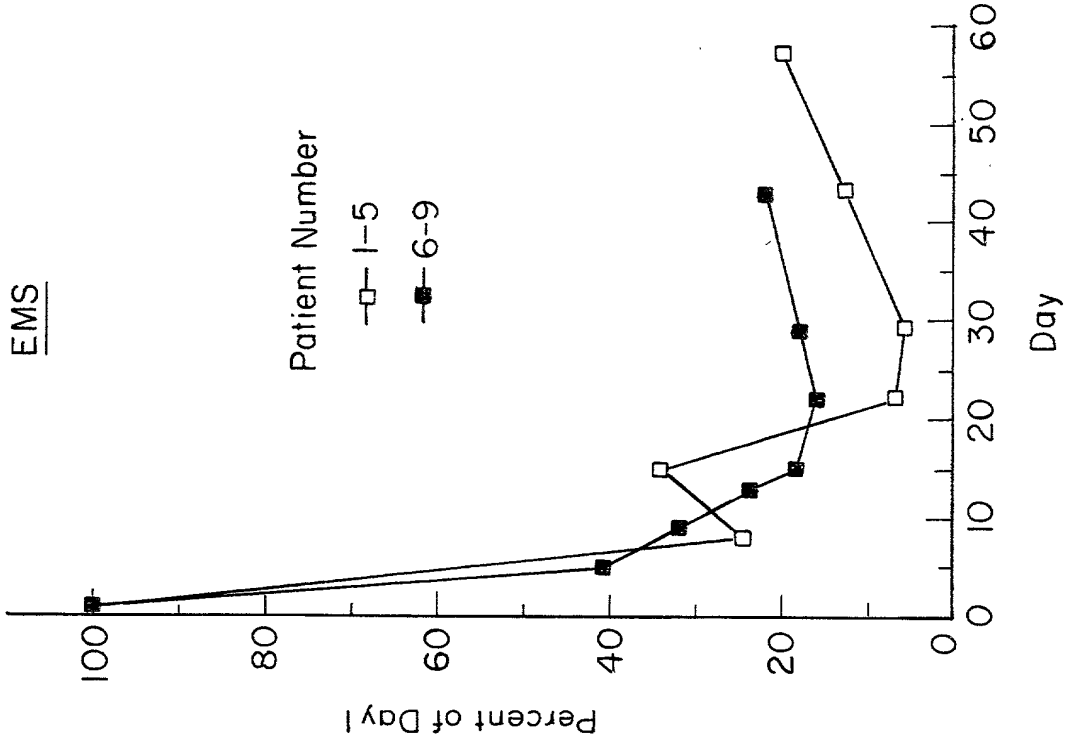

EMS
Patient Number
1-5
6-9
Percent of Day 1
Day
0
10
20
30
40
50
60
20
40
60
80
100

FIG. 17

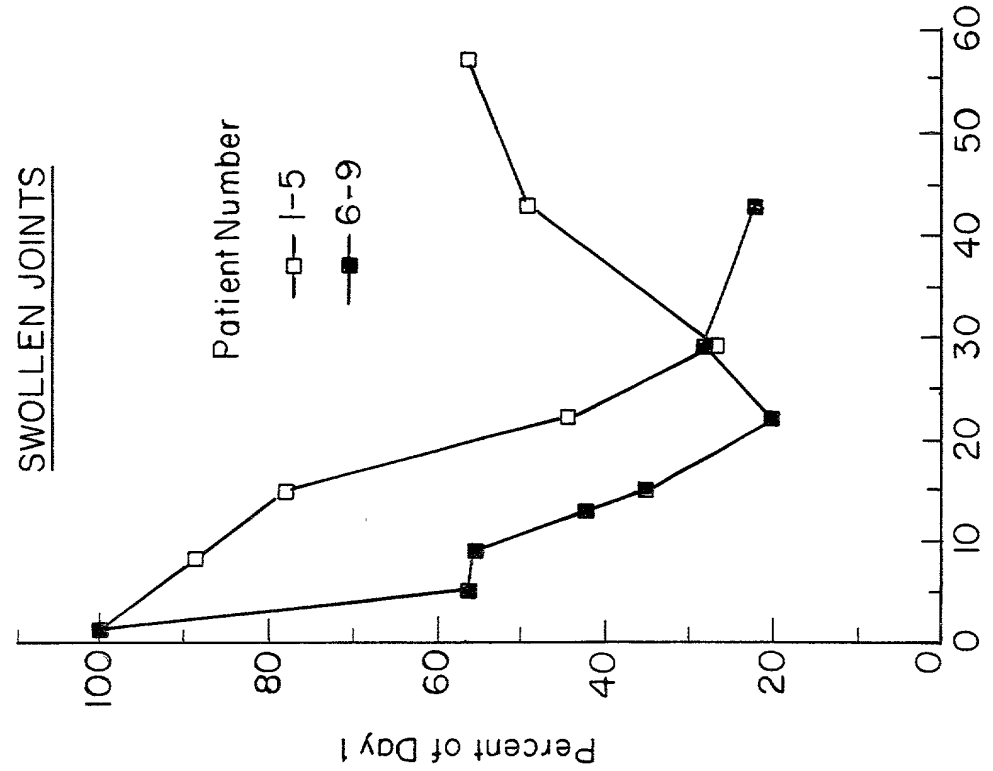

SWOLLEN JOINTS
Patient Number
1-5
6-9
Percent of Day 1
Day
0
20
40
60
80
100
10
30
50

FIG. 20

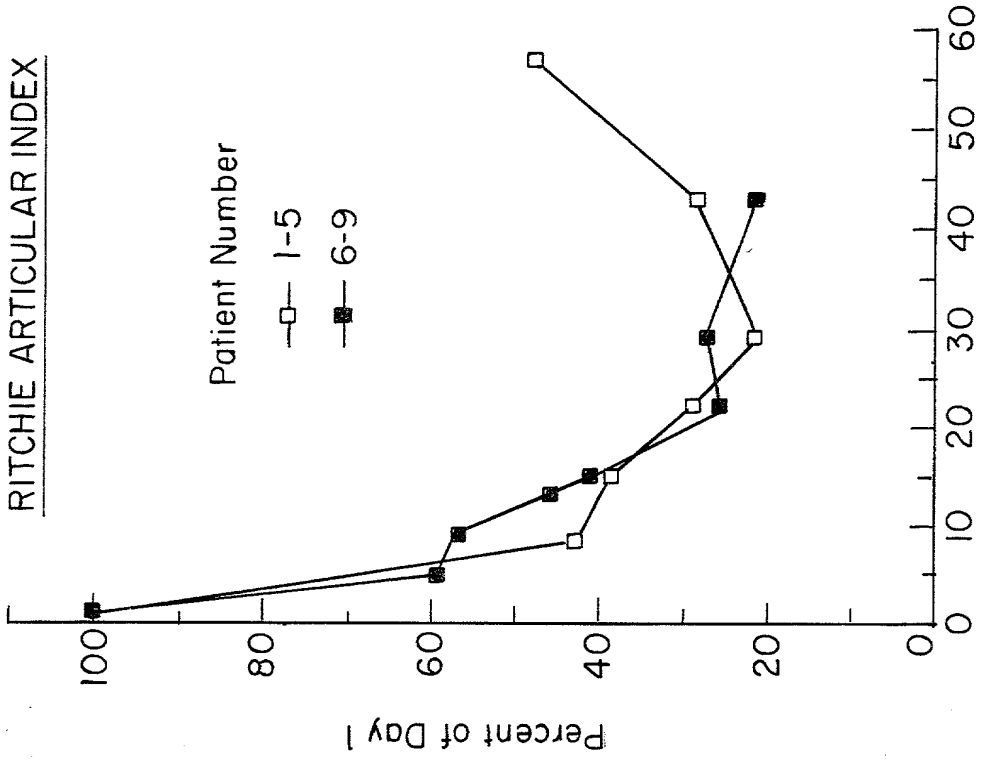

RITCHIE ARTICULAR INDEX
Patient Number
1-5
6-9
Percent of Day 1
Day
0
20
40
60
80
100
10
30
50

FIG. 19

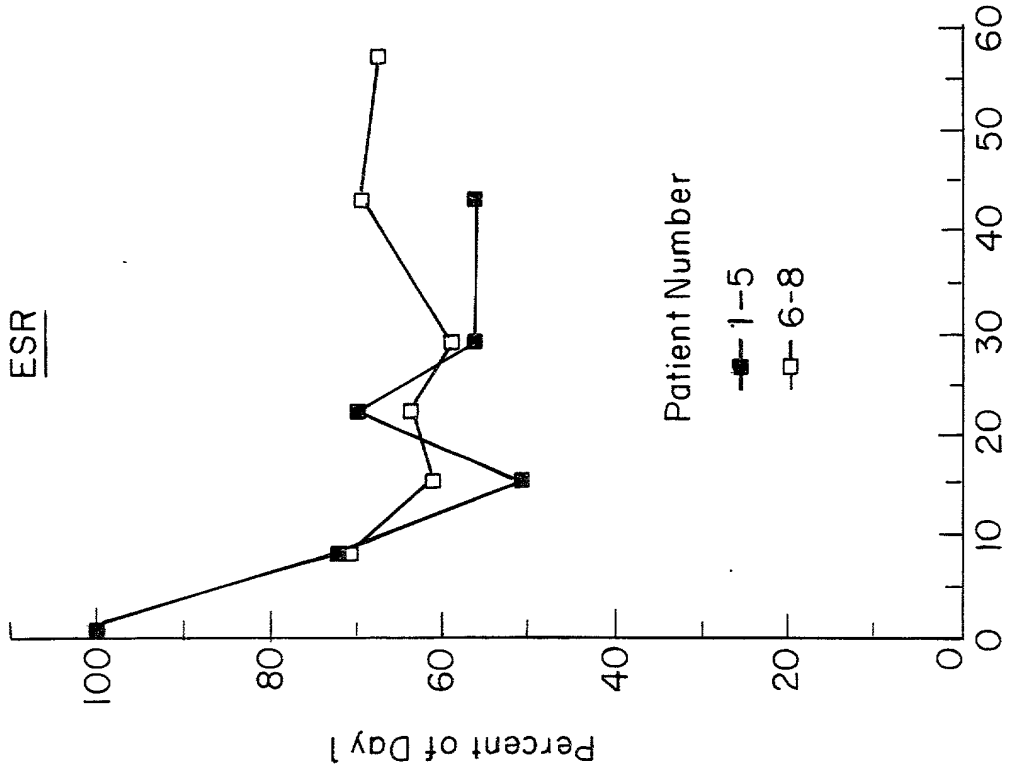

ESR
Percent of Day 1
100
80
60
40
20
0
0
10
20
30
40
50
60
Day
Patient Number
1-5
6-8

FIG. 22

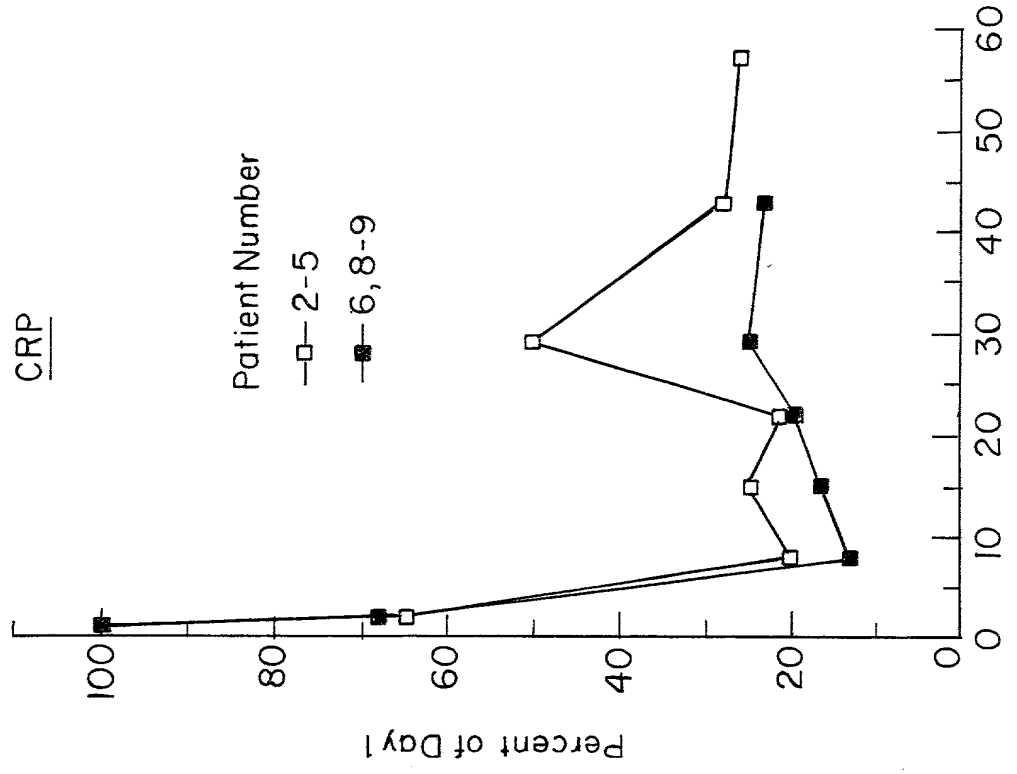

CRP
Percent of Day 1
100
80
60
40
20
0
0
10
20
30
40
50
60
Day
Patient Number
2-5
6, 8-9

FIG. 21

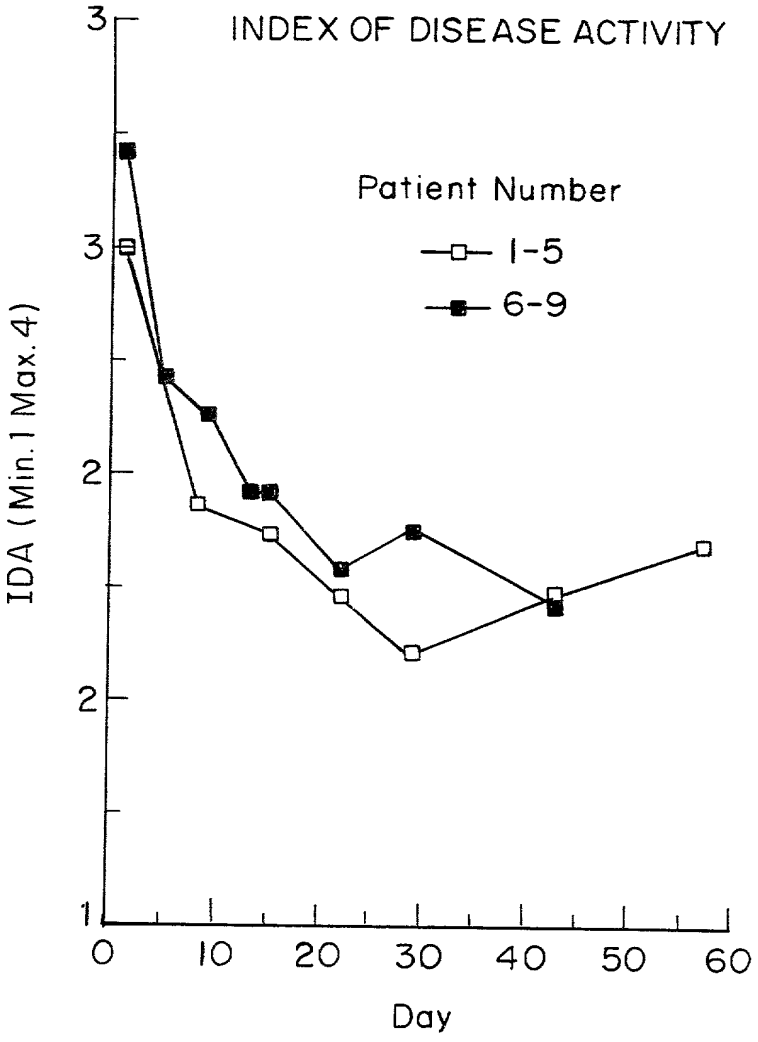

INDEX OF DISEASE ACTIVITY
Patient Number
1-5
6-9
IDA (Min. 1 Max. 4)
3
3
2
2
1
0
10
20
30
40
50
60
Day

FIG. 23

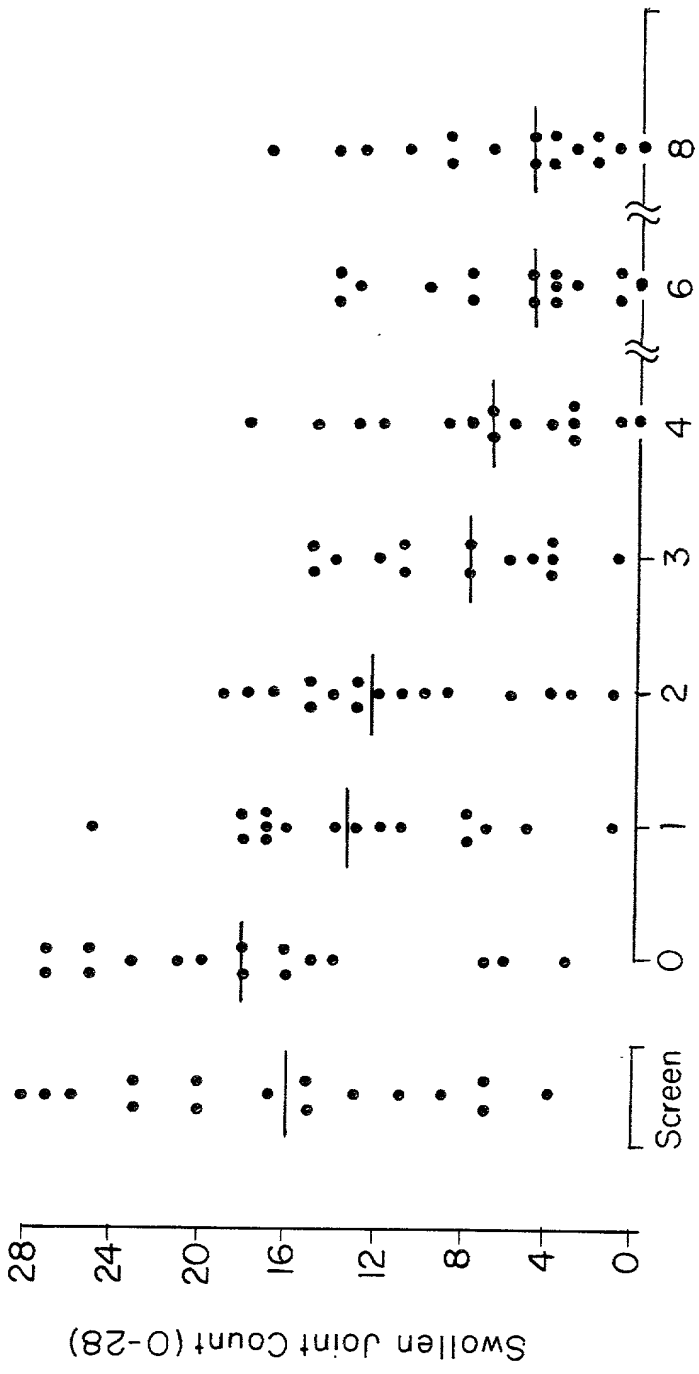

Swollen Joint Count (0-28)
28
24
20
16
12
8
4
0
Screen
0
1
2
3
4
6
8
Weeks

FIG. 24

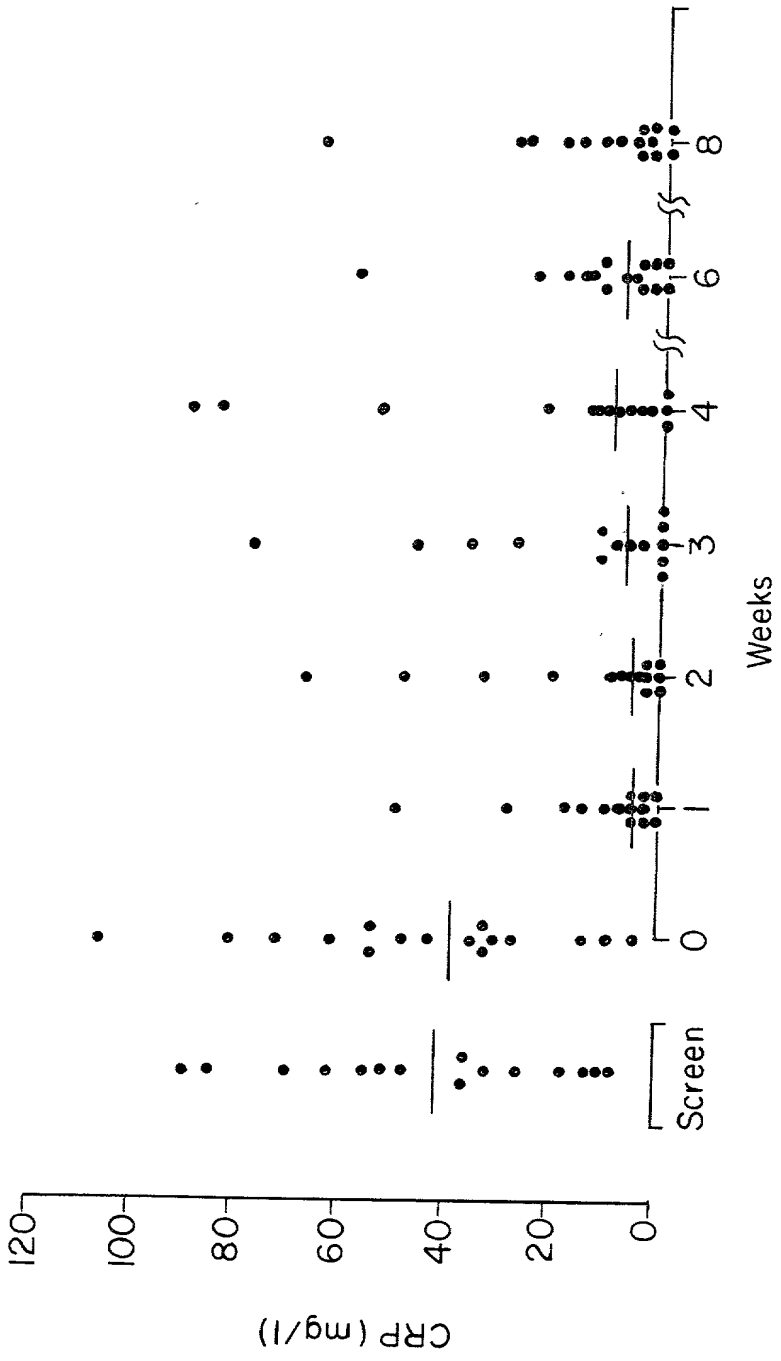


FIG. 25

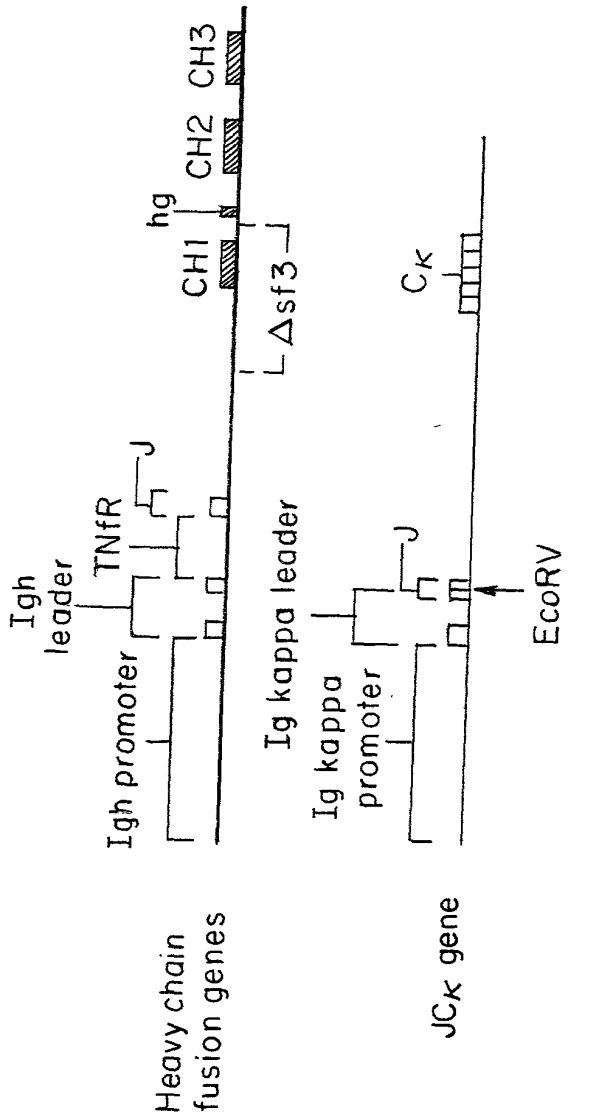

Heavy chain fusion genes
Igh promoter
Igh leader
TNfR
J
hg
CH1
CH2
CH3
Δsf3
Ig kappa promoter
Ig kappa leader
J
EcoRV
Cκ
JCκ gene

FIG. 26A

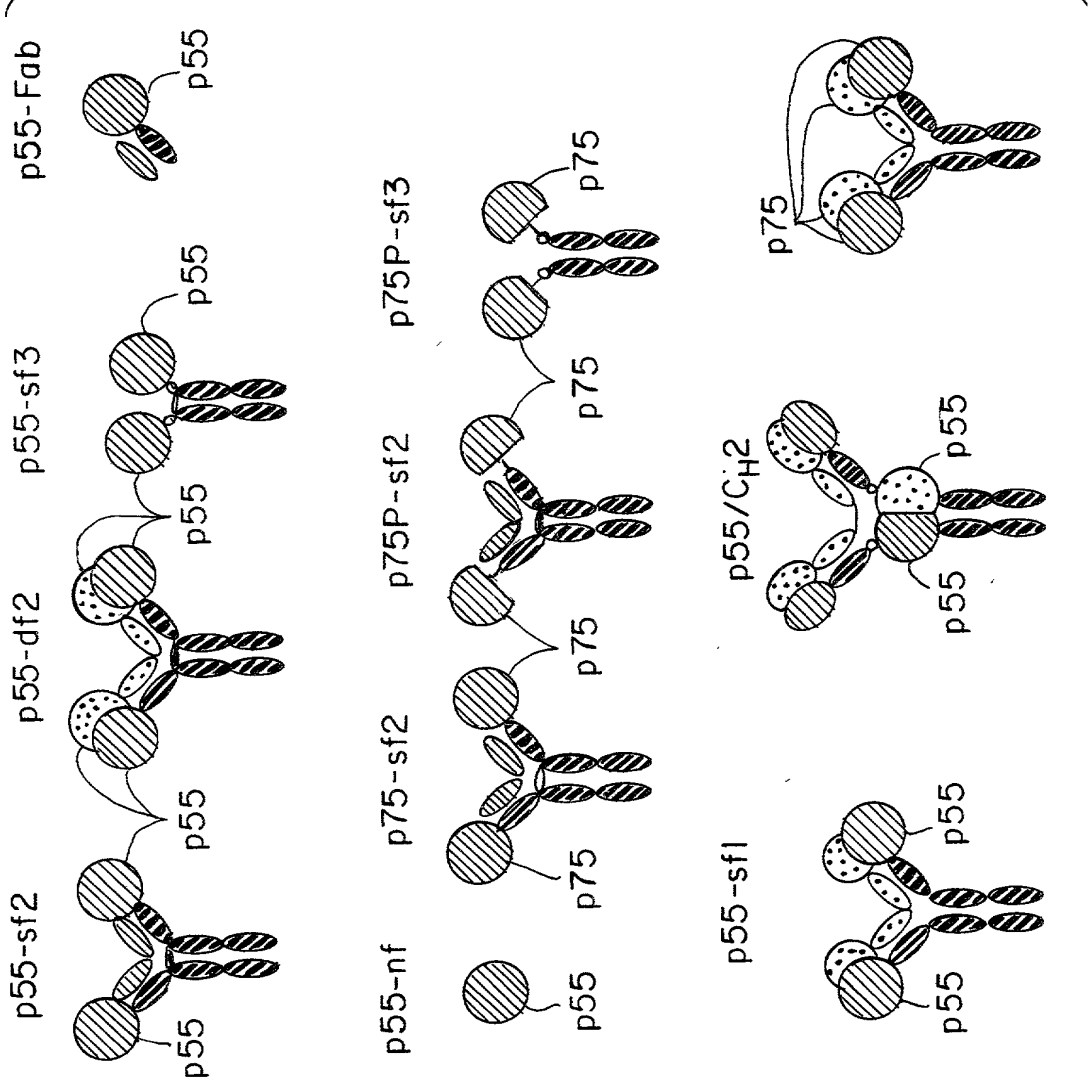

p55-Fab
p55
p55-sf2
p55-df2
p55-sf3
p55
p55
p55
p55
p55-nf
p75-sf2
p75P-sf2
p75P-sf3
p75
p75
p75
p75
p75
p55-sf1
p55/CH2
p75
p55
p55
p55
p55

FIG. 26B

3007TD 95162907

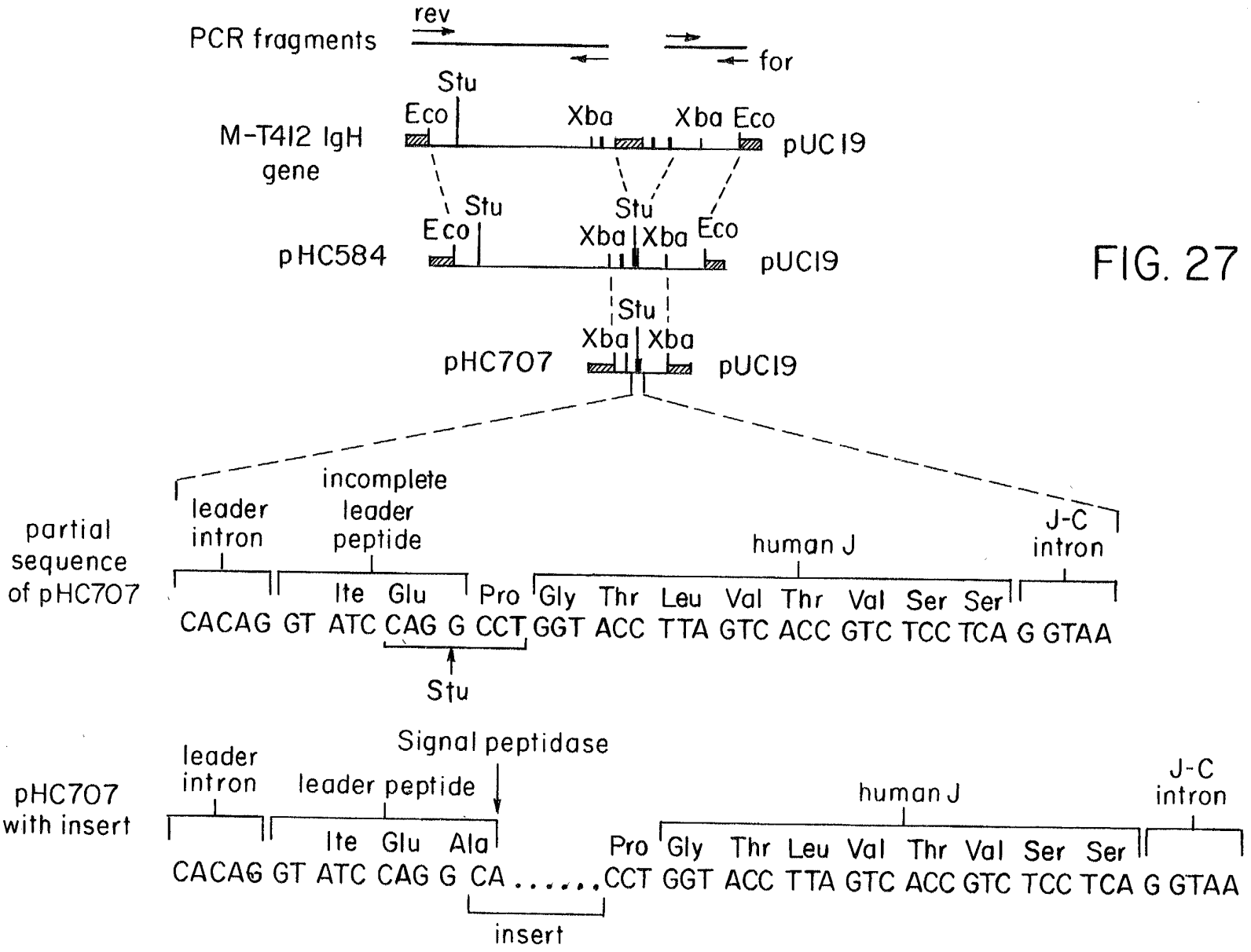


FIG. 27

Docket No.: 0975.1005-018
Title: METHODS OF TREATING HEPATITIS ....
Inventors: Junming Le, *et al*

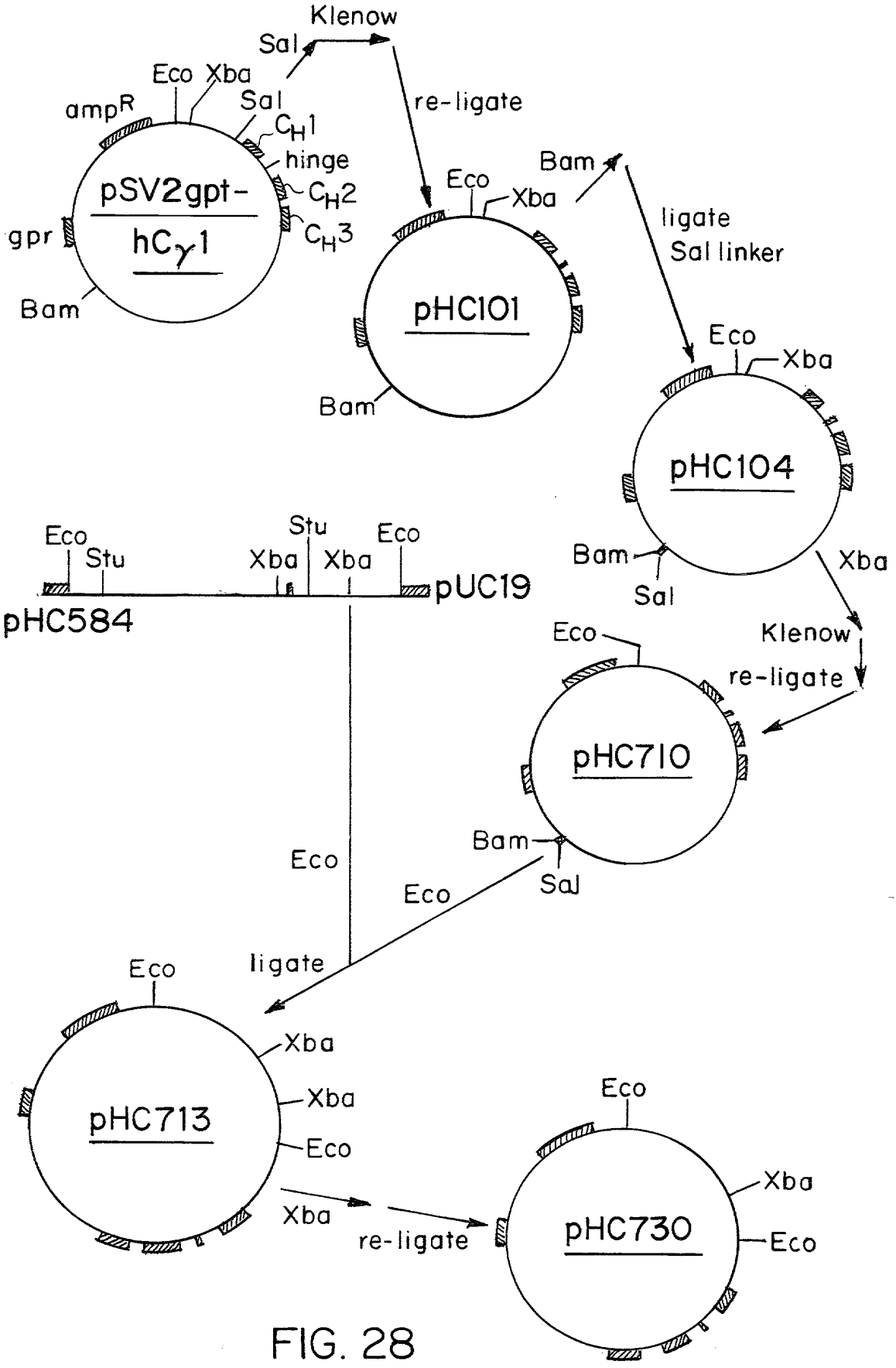

Klenow
Sal
Eco Xba
Sal
ampR
C_H1
hinge
C_H2
C_H3
pSV2gpt-
hCγ1
gpr
Bam
re-ligate
Eco
Xba
pHC101
Bam
Bam
ligate
Sal linker
Eco
Xba
pHC104
Bam
Sal
Xba
Klenow
re-ligate
Eco
pHC710
Bam
Sal
Eco
Stu
Eco
Xba
Xba
pUC19
pHC584
Eco
Eco
ligate
Eco
Xba
Xba
Eco
pHC713
Xba
re-ligate
Eco
Xba
pHC730
Eco

FIG. 28

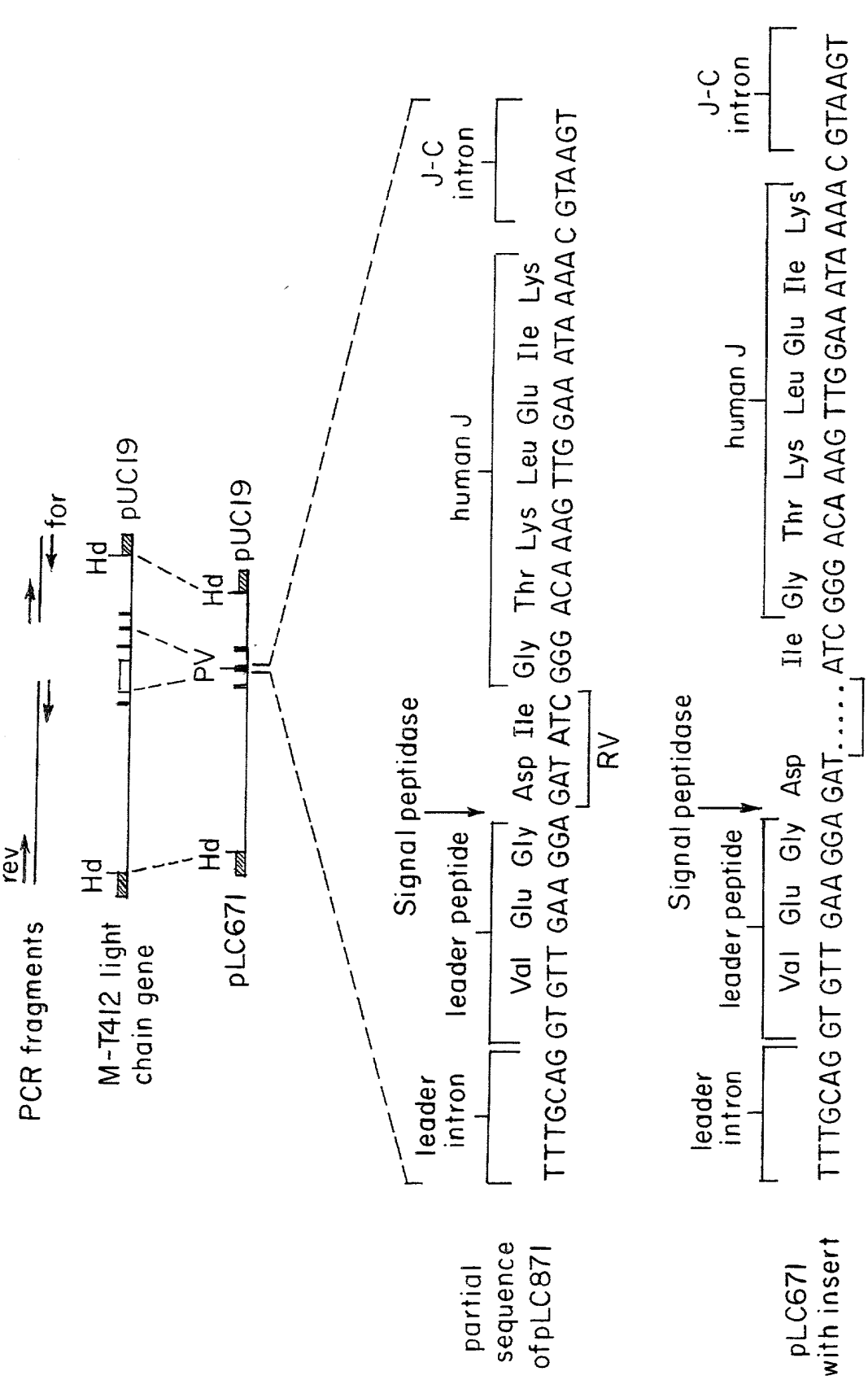

PCR fragments
rev
for
M-T412 light chain gene
Hd
Hd
pUC19
PV
Hd
pUC19
pLC671
partial sequence of pLC871
leader intron
Signal peptidase
leader peptide
human J
J-C intron
Val Glu Gly Asp Ile Gly Thr Lys Leu Glu Ile Lys
TTTGCAG GT GTT GAA GGA GAT ATC GGG ACA AAG TTG GAA ATA AAA C GTAAGT
RV
pLC671 with insert
Ile Gly Thr Lys Leu Glu Ile Lys
TTTGCAG GT GTT GAA GGA GAT.....ATC GGG ACA AAG TTG GAA ATA AAA C GTAAGT
insert

FIG. 29

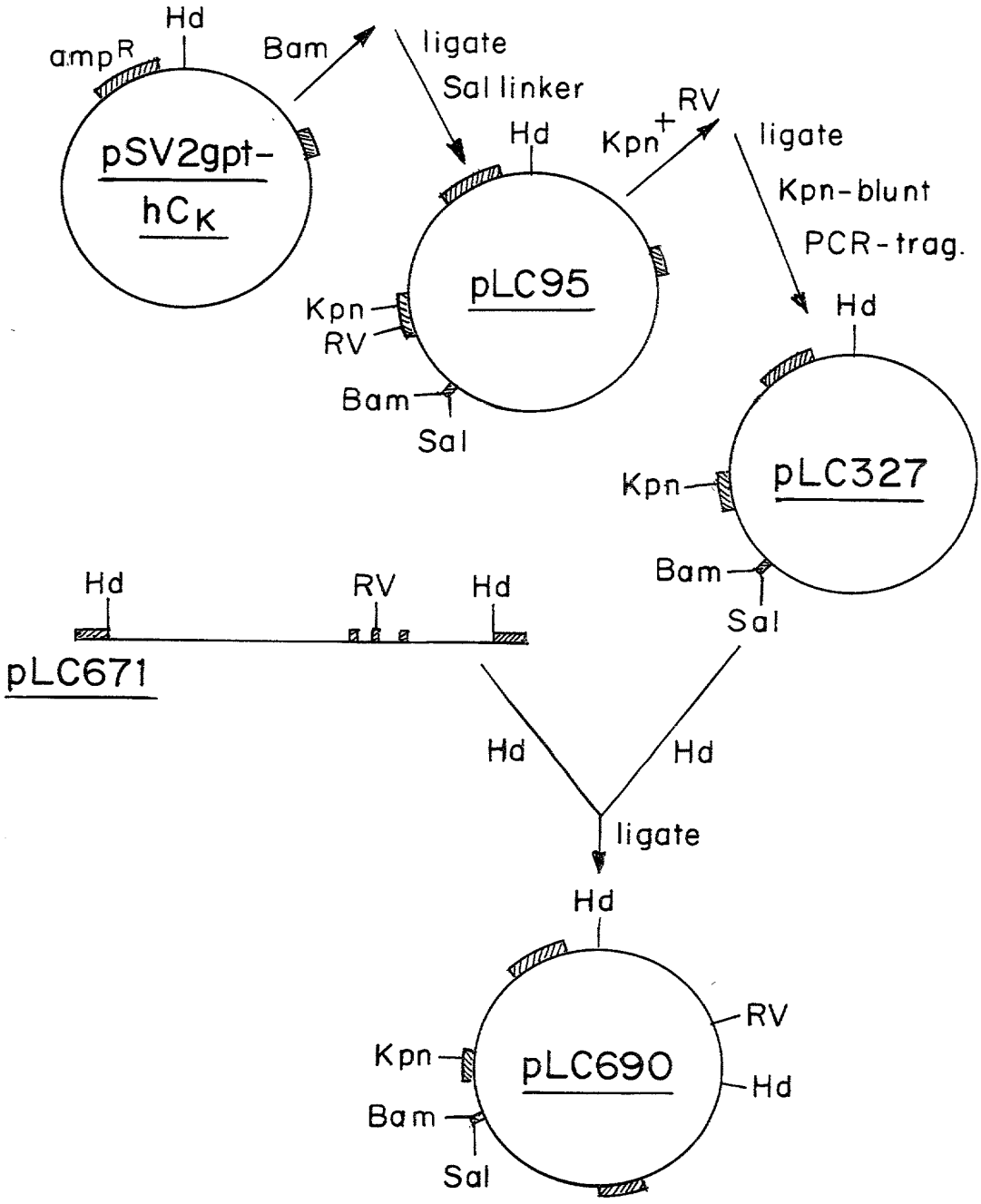

Hd
ampR
Bam
ligate
Sal linker
pSV2gpt-
hCK
Hd
Kpn+
RV
ligate
Kpn-blunt
PCR-trag.
pLC95
Kpn
RV
Bam
Sal
Hd
pLC327
Kpn
Bam
Sal
Hd
RV
Hd
pLC671
Hd
Hd
ligate
Hd
RV
Kpn
pLC690
Hd
Bam
Sal

FIG. 30

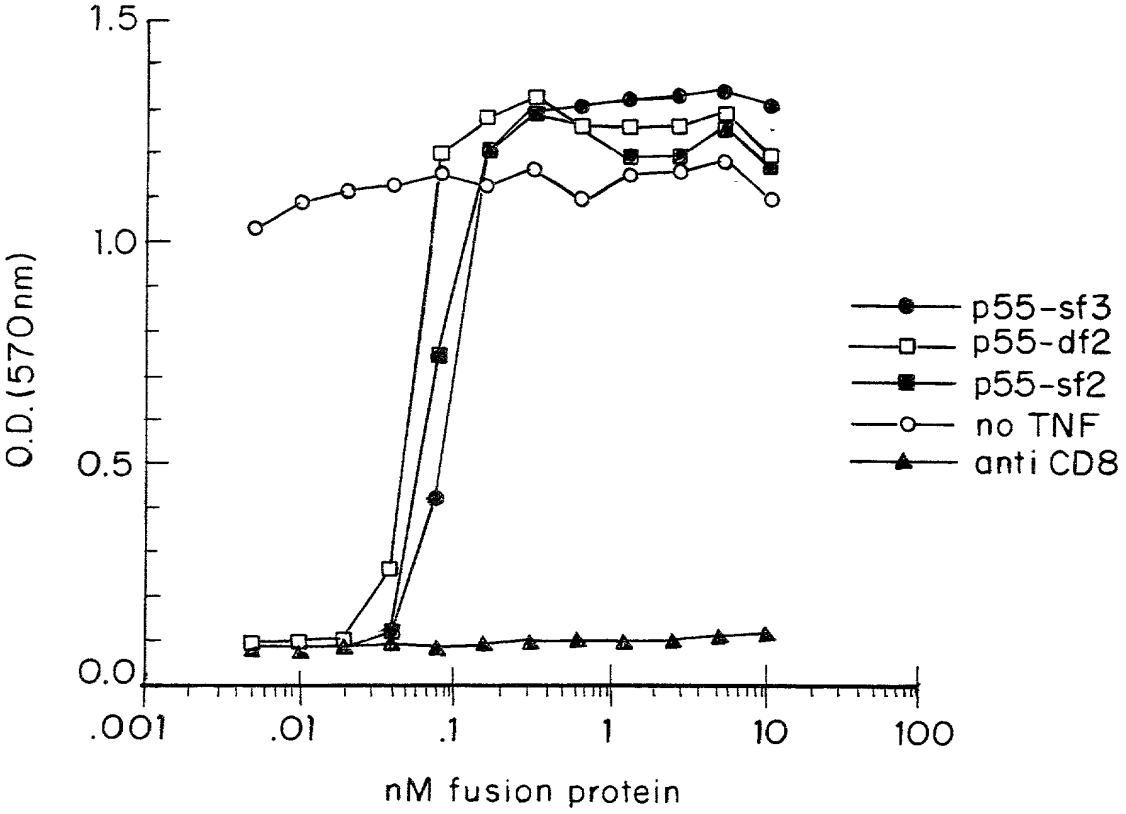

1.5
1.0
0.5
0.0
O.D.(570nm)
.001
.01
.1
1
10
100
nM fusion protein
p55-sf3
p55-df2
p55-sf2
no TNF
anti CD8

FIG. 31A

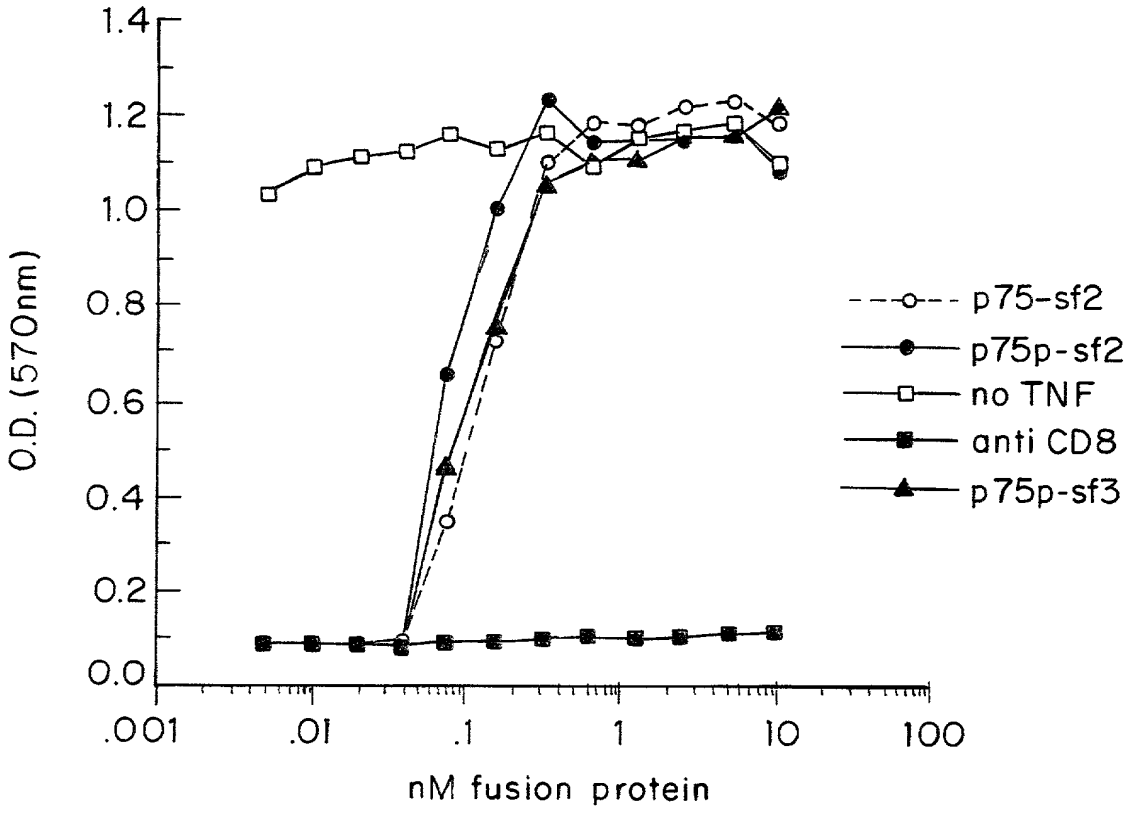

1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
O.D. (570nm)
.001
.01
.1
1
10
100
nM fusion protein
p75-sf2
p75p-sf2
no TNF
anti CD8
p75p-sf3

FIG. 31B

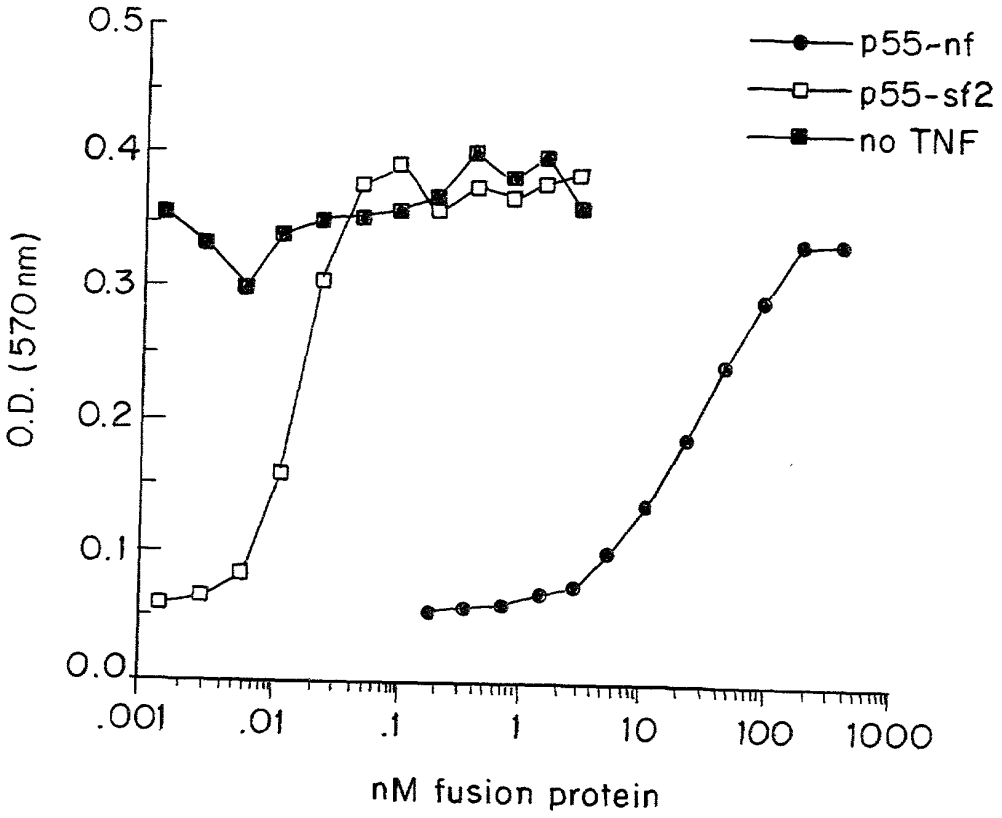

0.5
0.4
0.3
0.2
0.1
0.0
O.D. (570nm)
.001
.01
.1
1
10
100
1000
nM fusion protein
p55-nf
p55-sf2
no TNF

FIG. 31C

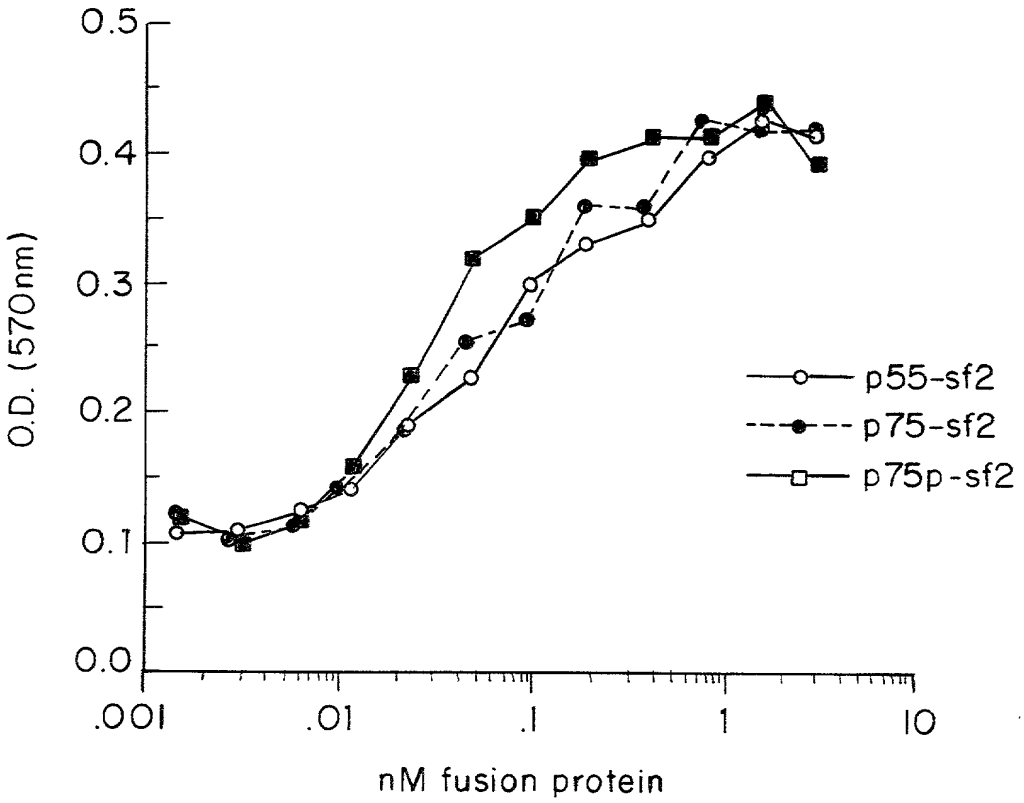

0.5
0.4
0.3
0.2
0.1
0.0
O.D. (570nm)
.001
.01
.1
1
10
nM fusion protein
p55-sf2
p75-sf2
p75p-sf2

FIG. 32

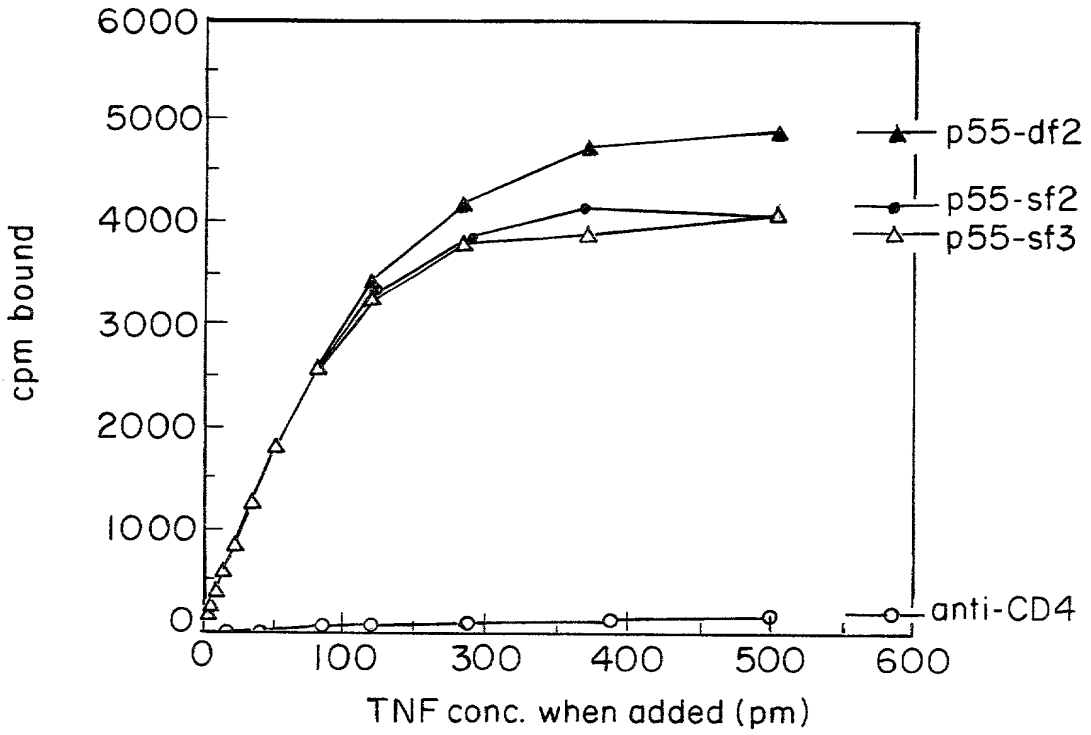


FIG. 33A

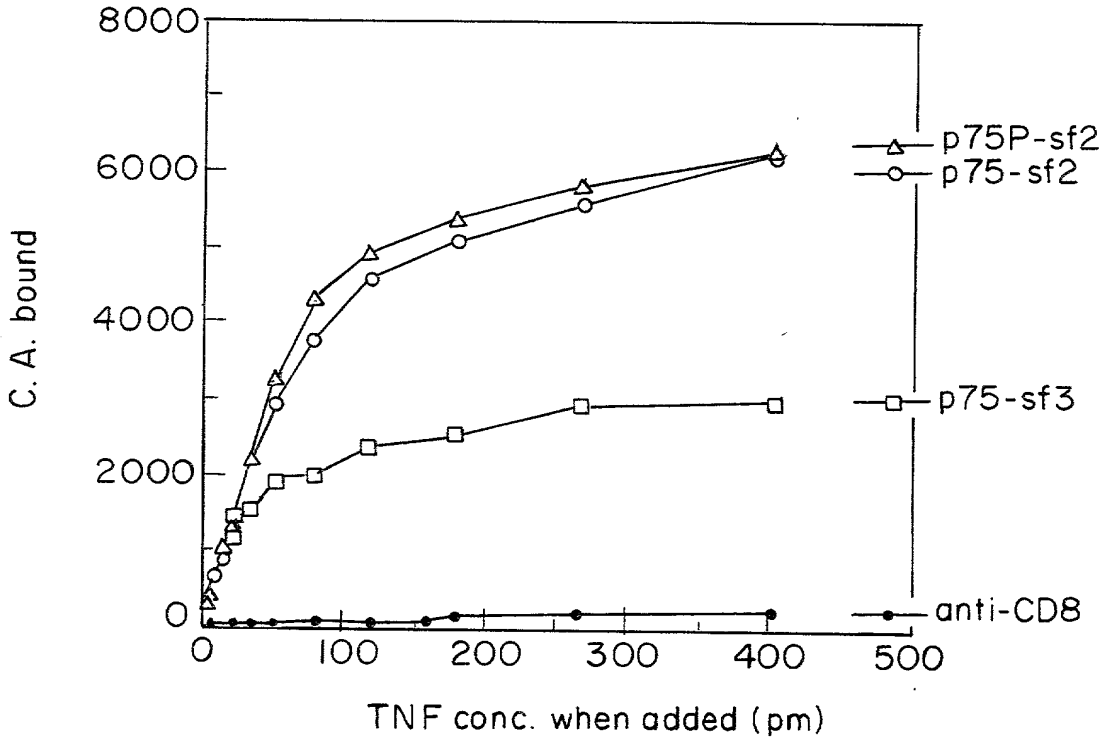


FIG. 33B

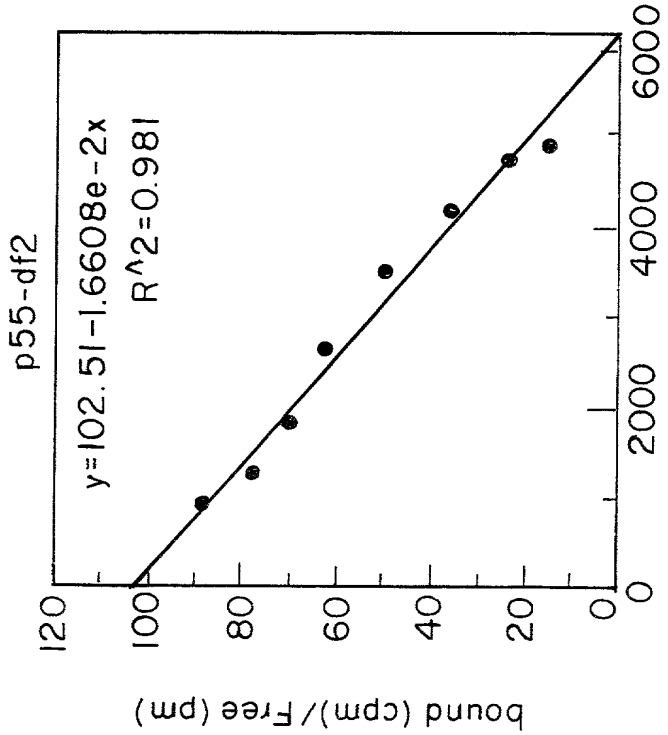


FIG. 33D

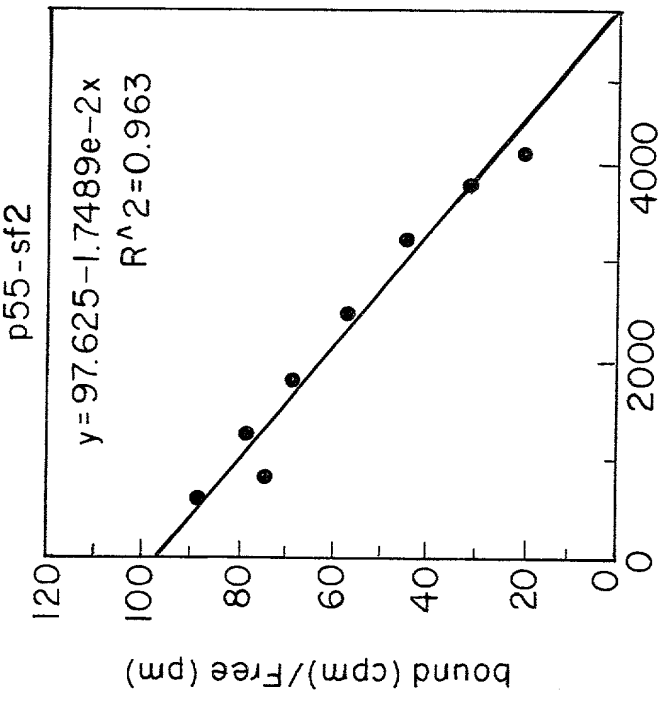


FIG. 33C

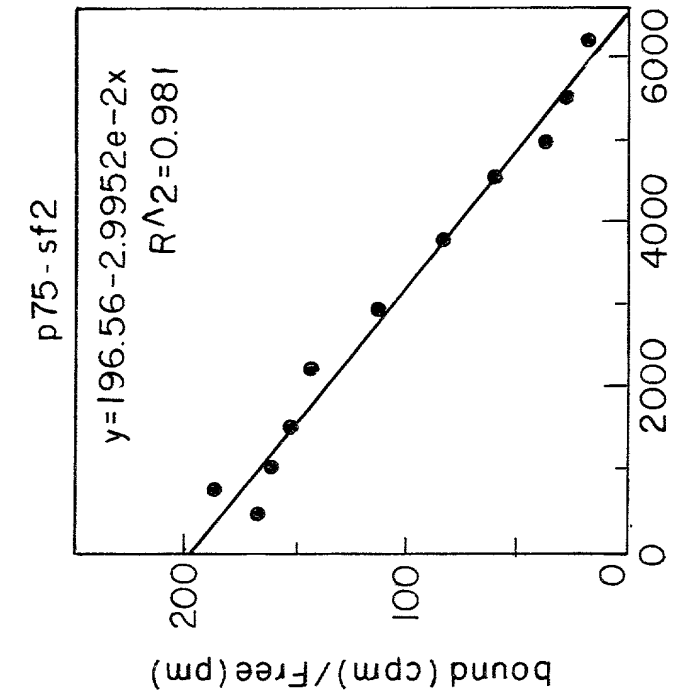


FIG. 33F

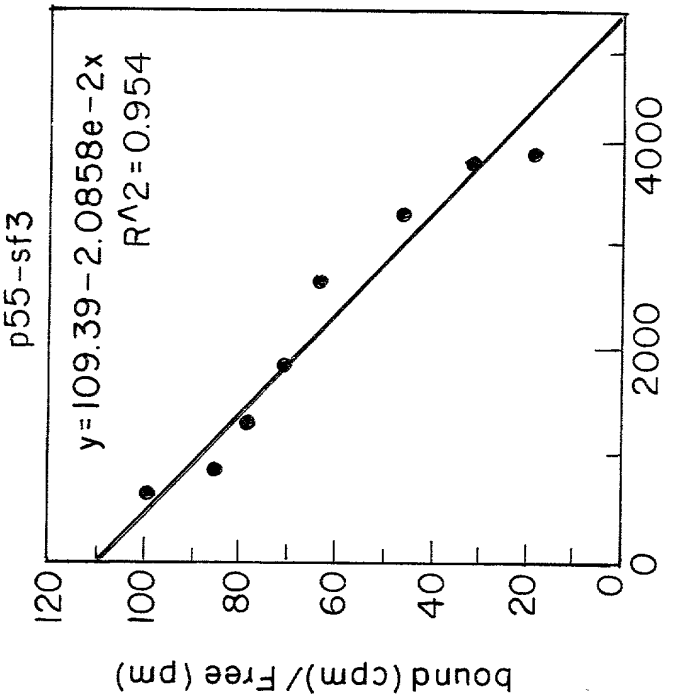


FIG. 33E

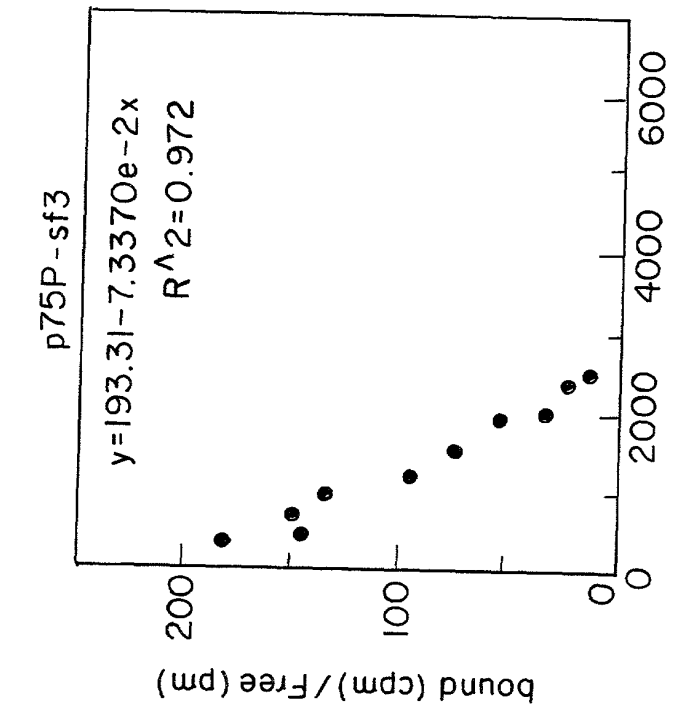


FIG. 33H

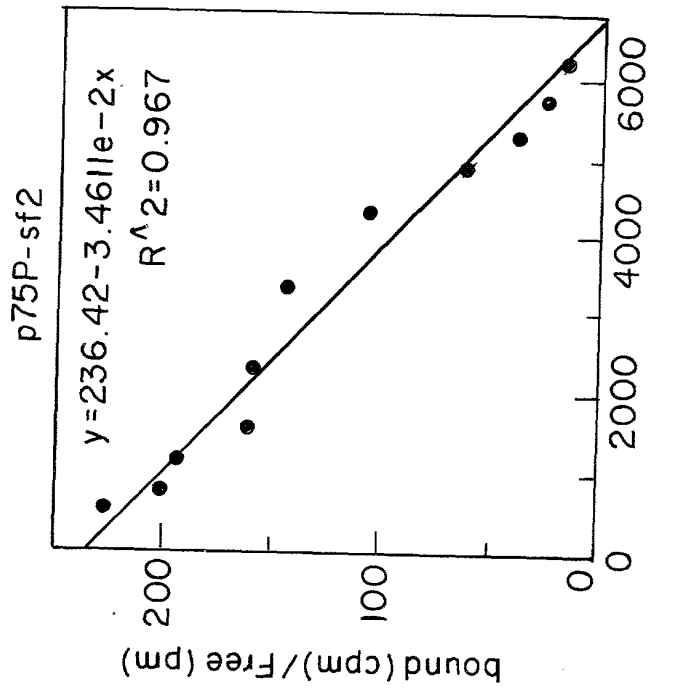
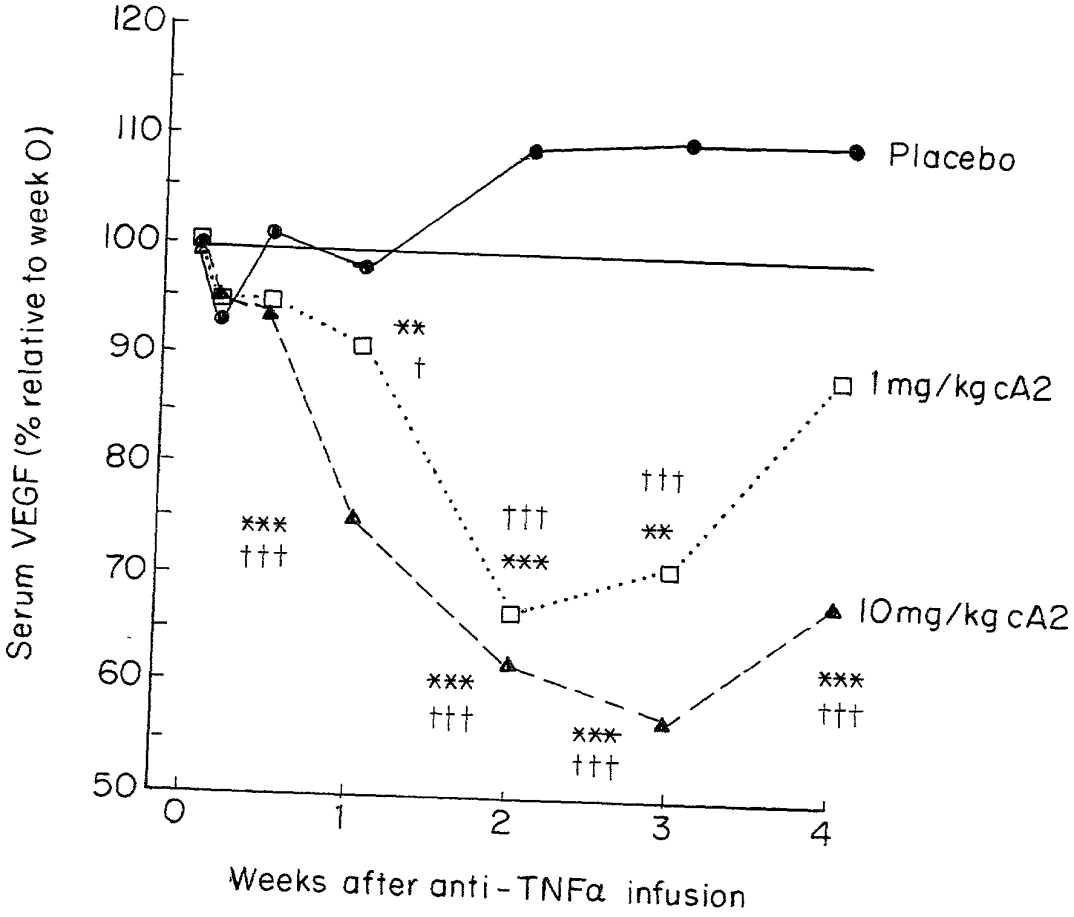


FIG. 33G



* p≤0.05, ** p≤0.01, *** p≤0.001 *versus* pre-infusion
† p≤0.05, †† p≤0.01, ††† p≤0.001 *versus* change in placebo group

FIG. 34